1958

Mechanism of the reaction of diazomethane with 2,4-pentanedione and synthesis of sterically-hindered beta-diketones

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MECHANISM OF THE REACTION OF DIAZOMETHANE WITH 2,4-PENTANEDIONE and SYNTHESIS OF STERICALLY-HINDERED BETA-DIKETONES

by

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A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

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Signature was redacted for privacy.

Dean of Graduate College

Iowa State College
1958

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PART I. MECHANISM OF THE REACTION OF DIAZOMETHANE WITH 2,4-PENTANEDIONE

Introduction

A study of the mechanism of the reaction of diazomethane with 2,4-pentanedione is described. Certain features of the mode of reaction in this system are elucidated. It might be expected a priori, that the passage of reactants to products could proceed by two pathways. One mechanism would involve encounter of the reactants, transfer of a proton, and collapse of the resulting ion-pair before the ions were separated by diffusion. In the other, after proton transfer, the species resulting could diffuse apart, thus becoming free to react also with other constituents of the medium.

The mechanism of any reaction is intrinsically of interest. In addition, this reaction is of interest since it represents one extreme in the general problem of carbon versus oxygen alkylation in ambident nucleophiles. In the reactions of diazomethane with beta-diketones, oxygen alkylate is essentially the only product. Details of mechanism in this reaction may lend insight into alkylation in other systems where mixtures of the alkylates are found.

Further, the use of diazomethane has been proposed as an analytical tool for the "determination of active hydrogen" (1).

The validity of the method depends upon an assumption about the mechanism of reaction of diazomethane with systems containing active hydrogen. This assumption is based on a considerable amount of empirical knowledge of a variety of systems. It would be of interest to attempt to extrapolate conclusions from a single, careful study to other reactions of diazomethane.

Historical

The reaction of diazomethane with 2,4-pentanedione can be classified as a reaction of an alkylating agent with an acid. More specifically, it is the reaction of a diazoalkane with a beta-diketone, a substance capable of coexisting in two tautomeric forms. There are, in the literature, some reports of studies of the alkylation of 2,4-pentanedione and analogous substances, which provide significant clues to mechanism(s). Some of these are reviewed here briefly.

The relationship between the rates of reactions of a variety of diazomethane derivatives with substituted acetic acids in cumene and the strength of the acids was reported by Staudinger et al. (2). In general, the stronger acids gave more rapid reactions. A similar phenomenon was noted in the reactions of di-p-tolyldiazomethane with substituted benzoic acids in benzene, toluene, and ethyl acetate (3).

Roberts et al. (4) has correlated the rates of reaction of diphenyldiazomethane with a number of substituted benzoic acids in ethanol with the strength of the acids. They used this correlation to obtain some previously unassigned Hammett substituent (sigma) constants (5,6).

In a detailed study of mechanism, Roberts found that the p-toluenesulfonic acid catalysed reaction of diphenyldiazomethane with ethyl alcohol exhibited general acid catalysis. In contrast, the reaction of ethyl diazoacetate with water

showed specific hydronium-ion-catalysis (7). The p-toluene-sulfonic acid-catalysed reaction of ethyl diazoacetate with ethanol (8) had different solvent and hydrogen isotope effects from the formally similar reaction with diphenyldiazomethane. Deuterium-exchange experiments indicated that rapid and reversible equilibrium was established between ethyl diazoacetate and its conjugate acid ($+N_2CH_2CO_2C_2H_5$). Similarly, equilibration occurred during the reaction of ethyl diazoacetate with acetic acid in the absence of strong acid, both in pure acetic acid and in benzene solution. Roberts concluded that general-acid-catalysed and specific-oxonium-catalysed reactions of diazo compounds involved different mechanisms.

In the study of the reaction of diphenyldiazomethane with benzoic acid in ethanol, Roberts et al. (9) demonstrated that the mechanism was one of direct reaction between a molecule of diphenyldiazomethane and a molecule of benzoic acid, rather than a multi-step process involving intermediates. In this system, diphenyldiazomethane reacts simultaneously with the solvent (ethanol) by the general-acid-catalysed process.

The principal evidence for the one-step mechanism in the reaction of benzoic acid with diphenyldiazomethane consists of the effect of various added nucleophiles on the relative amounts of the products, benzhydryl ethyl ether and benzhydryl benzoate, formed. Neither iodide nor benzoate ions affect the product ratio. Thiocyanate ion changes the product ratio, as

indicated by an increase in the consumption of benzoic acid without alteration of the overall rate of disappearance of the diazo compound.

Acetic acid and 2,4-dinitrophenol behave similarly to benzoic acid in their reactions with diphenyldiazomethane in ethanol (10,11).

Recently Hancock and Westmoreland (12,13) have correlated Hammett substituent constants with rates of reactions between a number of substituted diphenyldiazomethanes and substituted benzoic acids in toluene at 25°. The effects of m- and p-substituents on the reactivity of the diphenyldiazomethanesis independent of the effects of m- and p-substituents in the benzoic acid.

The rates of the reactions of diazomethane and 2-diazopropane with two acids, acetic acid and formic acid, have been studied (14). A novel technique, involving measurement of the intensity of microwave absorption by the diazoalkanes, was used to follow the reactions.

The rates of the methylation of 2,4-pentanedione in acetone using methyl iodide and an alkali carbonate have been measured (15). In the reaction, carbon-alkylation occurs, and the mono- and di-alkylate were formed in consecutive, competive reactions. Having separated the rates of the consecutive reactions, Brandstrom found that the rate of the monomethylation was first order with respect to methyl iodide, irrespec-

tive of the nature of the metal carbonate. The same was true for the second alkylation step in the presence of sodium or potassium carbonate. In the presence of rubidium or cesium carbonate the rate depended on 2,4-pentanedione concentration as well as on methyl iodide concentration. The rates of reaction in the presence of the various alkali carbonates are quite different. The first step is twenty times faster in the presence of potassium carbonate than in the presence of sodium carbonate. Rubidium and cesium carbonate increase the rates by another factor of ten. Variations in the rate of the second alkylation were even larger.

Eistert et al. (16,17,18) used diazomethane as a structural probe in the study of symmetrical and unsymmetrical beta-diketones. His conclusions about configuration of the diketones are inferred from variations in reactivity and in reaction products as a function of the polarity of reaction media. These studies were complemented by spectral studies.

Two solid modifications of dibenzoylmethane exist. Eistert considers the lower melting compound to be an "open" cis-enol since it reacts much more rapidly with diazomethane in absolute ether than the higher melting compound. He designates the higher melting compound as the chelated cis-enol.

Only one solid modification of benzoylacetone exists. Eistert implies that a tautomeric mixture is formed in solution. In one tautomer the enolic proton is associated with the

oxygen of the benzoyl group, while in the other it is associated with the oxygen of the acetyl group. Both tautomers are believed to be chelated cis-enols. This inference was drawn from much the same sort of evidence as was used in the study of dibenzoylmethane.

Eistert's conclusions are based on the assumption that diazomethane reacts in a smoothly concerted mechanism at the site of attachment of the hydrogen atom. Arndt has suggested such a mechanism (1). Huisgen (19,20) has pointed out that a concerted mechanism could be distinguished from an "oriented ion-pair mechanism" only with difficulty.

From the reaction of diazomethane with 2,4-pentanedione, Eistert et al. (17,21) has isolated two methyl enol ethers. On the basis of the variations in the relative amounts of the two products formed under a variety of conditions and from the relative stabilities of the ethers, he designated one as the cis-enol ether and the other as the trans-enol ether.

Experimental

Materials

Diazomethane The procedure used for the preparation of solutions of diazomethane is the decantation method of Arndt (22a, p.166) with some modification. Five hundred milliliters of an 0.8 molar diazomethane solution were usually prepared. The diazomethane solution was always dried for three hours over potassium hydroxide pellets. The solution was then stored in a refrigerator at -15° to -20° until use (usually within two to three days). In benzene solutions the solvent solidified so that two to three hours had to be allowed for the solution to warm up. The solutions of diazomethane were used without purification by distillation. All glassware involved, from the flask in which the diazomethane stock solution was stored to the volumetric flasks in which the reactions were carried out, were washed with concentrated ammonium hydroxide and allowed to dry in an oven at 140°. This procedure was to rid the glass surface of any trace of acid which would catalyse the decomposition of the diazomethane. Goubeau and Rohwedder (22b) have observed that ground glass joints washed with sodium-dried benzene do not cause the catalysed decomposition of diazomethane usually associated with rough surfaces.

The above procedure cannot be used for preparing diazomethane solutions in solvents which are miscible with water. A solution of diazomethane in 1,2-dimethoxyethane was prepared by

passing a stream of nitrogen through a solution of diazomethane in xylene (contained in a two-necked flask) up through a condenser and U-tube and into a flask containing 1,2-dimethoxyethane, the latter being cooled in a crock of ice. The xylene solution was heated during passage of the nitrogen.

Although there are other precursors to diazomethane, nitrosomethylurea was chosen because of its ease of preparation in large quantities and its stability in storage. The procedure for the preparation of nitrosomethylurea was that of Arndt (23, p.461).

2,4-Pentanedione 2,4-Pentanedione (Eastman White Label) was distilled at atmospheric pressure through a tantalum spiral wire column, 74 centimeters long and 7 millimeters in diameter. The middle third of the fraction boiling from 134° to 135° was retained and redistilled. A fraction, constituting the middle third of the redistilled material, was collected and stored at -20° until use (two to three days at most). The refractive indices at 25° and neutralization equivalents for three different samples of doubly distilled diketones were: 1.4516, 100.5%; 1.4496, 99.9%; 1.4492, 98.9%. The neutralization equivalents were determined by weighing samples of the diketones into pyridine and titrating with standard n-butyltriethylammonium hydroxide. The refractive indices can be compared with the value reported in the literature; n_D^{25}1.4500(24).

p-Toluenesulfonic acid p-Toluenesulfonic acid (Eastman Kodak, 90%) was recrystallized from ether - benzene until no tinge of color remained (usually two to three times). Roughly one milliliter of benzene and five milliliters of ether were used for each gram of the sulfonic acid. The hot solution of the sulfonic acid consisted of a water phase and an organic phase. The organic layer was decanted from the water phase during each filtration since it was observed that colored impurity tended to remain in the aqueous layer.

Boron trifluoride - 2,4-pentanedione reaction products Boron trifluoride reacts with 2,4-pentanedione in benzene to give difluoroboron acetylacetonate and hydrofluoric acid (25). Solutions which were about one molar in 2,4-pentanedione and one-quarter molar in strong acid were prepared in 1,2-dimethoxyethane by passing gaseous boron trifluoride (Matheson) through a flow meter into 1,2-dimethoxyethane contained in a trap cooled with a Dry Ice - acetone bath in a Dewar flask. The reaction solution was warmed to room temperature fairly rapidly and then allowed to react with diazomethane (in benzene). The reaction mixture of boron trifluoride and 2,4-pentanedione was colorless at first but within ten minutes changed to a yellow color which continued to increase in intensity with time. Hence, the reaction with diazomethane was carried out as soon as the boron trifluoride - 2,4-pentanedione solution had been warmed to room temperature.

Reaction solvents Benzene (Baker and Adamson reagent grade) was dried with sodium ribbon. 1,2-Dimethoxyethane (Ansul Ether Product No. 121) was refluxed over sodium for two days, distilled, and stored over sodium ribbon.

Some preliminary runs were made in diethyl ether - benzene solvent. The diethyl ether was Mallinckrodt anhydrous analytical reagent.

Titration solvents Non-aqueous titrations were carried out in acetone or pyridine as the solvent. Acetone (Baker and Adamson reagent grade) and pyridine (Fisher reagent grade) were used without further purification. Blank corrections were made which varied according to the system being titrated but never exceeded 0.08 milliliters.

Methanolic sodium hydroxide Stansol standard volumetric concentrate was diluted to the appropriate concentration with absolute methanol (Baker and Adamson reagent grade).

Tetra-alkylammonium hydroxide The use of tetra-alkylammonium hydroxides dissolved in methanol - benzene (1:10) as titrants in non-aqueous media was proposed by Fritz and Yamamura (26). Triethylamine (Eastman White Label) was heated under reflux for four to five hours with n-butyl iodide (Matheson). The triethyl-n-butylammonium iodide thus formed was filtered and recrystallized from absolute ethanol - ethyl acetate (140 grams of triethyl-n-butylammonium iodide in 500 milliliters of ethyl acetate and 110 milliliters of absolute

ethanol). The triethyl-n-butylammonium iodide (90 grams) was dissolved in absolute methanol (180 milliliters) and silver oxide (60 grams, Baker and Adamson, purified) was added to the solution. The mixture was agitated occasionally over a two to three hour period and the system kept cold with ice. The mixture was then filtered and the solid material was washed three times with cold benzene. The filtrate and washings were diluted with anhydrous benzene to 1600 milliliters of solution. The resulting solution was 0.1 molar in base.

Agitation is done in the cold to prevent formation of impurities, but also decreases the rate of conversion of the iodide to hydroxide. Triethyl-n-butylammonium bromide reacts more rapidly with the silver oxide (agitation time, one hour) but is formed much less readily from the amine and alkyl bromide. The best method for preparation of this tetra-alkylammonium hydroxide with a minimum of impurities will be published in the near future.*

Benzoic acid Baker reagent grade benzoic acid was used as the primary standard for the tetra-alkylammonium hydroxide titrant. All standardizations were done potentiometrically but it was found that meta-cresol purple is an excellent indicator. Thymolphthalein is also quite adequate. The titrations were performed in acetone as solvent under a cover of dry nitrogen.

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*Moye, Anthony J. and Fritz, J. S. Chemistry Department, Iowa State College, Ames, Iowa. Private communication. 1958

Benzoic acid was also used for standardization of methanolic sodium hydroxide, the titration being done in acetone under nitrogen. Here again meta-cresol purple can be used for the indicator. A better primary standard, however, for the methanolic sodium hydroxide is salicylic acid because a larger change in potential occurs at the end-point. Phenol red could possibly be used to give a fairly good estimate of the end-point.

Salicylic acid Baker reagent grade salicylic acid was used to standardize methanolic sodium hydroxide. A solution in anhydrous 1,2-dimethoxyethane was used to determine diazomethane in solution. The salicylic acid solutions were standardized using triethyl-n-butylammonium hydroxide as a secondary standard.

3-Methyl-2-4,pentanedione 3-Methyl-2,4-pentanedione was prepared according to the procedure of Hauser and Adams (27) from methyl ethyl ketone and acetic anhydride using boron trifluoride as a catalyst. The product, obtained in low yield, boiled at 65-67° at 30 mm. (lower than the boiling point reported by Hauser) and had an infrared spectrum very nearly identical with that reported for the compound by Gerald Guter (28, pp.39,40). Analysis by gas chromatography (DHF instrument) showed only traces of impurity. The position of a minor peak indicated that the principal impurity was 2,4-hexanedione. The ultraviolet spectrum of 3-methyl-2,4-pentanedione showed a maximum at 290 millimicrons with a log ϵ value of 3.54. The

compound decomposes on standing, turning yellow.

4-Methoxy-3-pentene-2-one A mixture produced by a reaction of diazomethane with 2,4-pentanedione was fractionally distilled in vacuo through a tantalum spiral wire column. The fraction boiling at 61-62° at 10-11 mm. was presumed to be 4-methoxy-3-pentene-2-one. Identification was based on comparison with physical properties reported for the compound by Eistert et al. (17). Their product was isolated from a similar reaction mixture and was believed to be the isomer in which the methoxyl and acetyl groups are trans to one another. The product contained small amounts of 2,4-pentanedione and 3-methyl-2,4-pentanedione as shown by analysis by gas chromatography on an Apiezon L column in the DHF instrument at 165°. The ultraviolet spectrum of this methyl enol ether showed a maximum at 255 millimicrons with a maximum value of log ϵ of 4.12.

4-Ethoxy-3-pentene-2-one A solution of diazoethane in diethyl ether was prepared by the action of aqueous potassium hydroxide on nitrosoethylurea*. A clear, orange solution (diazomethane is a golden yellow) was obtained. This solution was dried over potassium hydroxide pellets for slightly less than an hour since it appeared to be decomposing fairly rapidly (as evidenced by nitrogen evolution). 2,4-Pentanedione

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*The nitrosoalkylureas were made available through the generosity of Mr. W. A. Bappe who prepared the compounds from the corresponding ammonium chlorides and potassium cyanate.

was added (slowly) and nitrogen was evolved quite rapidly. The reaction mixture was allowed to stand overnight. The orange color disappeared during the period. The reaction mixture was concentrated by removal of the solvent and some of the unreacted 2,4-pentanedione by distillation. The residual solution was then analysed by gas chromatography on an Apiezon M column at 167° in the DHF instrument. There were two major peaks, one of which could be assigned to 2,4-pentanedione. The other was assumed to be the ethyl enol ether of 2,4-pentanedione, i.e., 4-ethoxy-3-pentene-2-one. The retention time was taken for a standard for detection of ethyl enol ether in mixtures produced by reactions of diazomethane with 2,4-pentanedione. Since there were but small amounts of other impurities present, no attempt was made to isolate and purify the compound by conventional techniques.

4-Butoxy-3-pentene-2-one A solution of diazobutane in diethyl ether (a deep orange) was prepared in a manner similar to that described above for the preparation of diazoethane. Reaction of diazobutane with 2,4-pentanedione was quite vigorous. Only small amounts of impurity were present in addition to unreacted 2,4-pentanedione as shown by gas chromatographic analysis. The product was assumed to be 4-butoxy-3-pentene-2-one and its retention time, somewhat more than double that of the ethyl enol ether, was used for detection of the n-butyl enol ether of 2,4-pentanedione.

Gas chromatographic analysis of the diazobutane - 2,4-pentanedione reaction mixture after one week gave essentially the same results as were obtained after one day. After a month the composition of the mixture had changed as indicated by growth of formerly minor peaks.

2,4-Hexanedione Ethyl acetate (reagent grade) and methyl ethyl ketone were condensed in the presence of sodium ethoxide (prepared by the action of sodium hydride on ethanol). The solvent was removed and the reaction mixture analysed by gas chromatography (Apiezon M column at 167° in the DHF instrument). Two major products were obtained along with considerable amounts of other minor impurities. The product present in smaller amount was presumed to be 3-methyl-2,4-pentanedione on the basis of its retention time. The major product was assumed to be 2,4-hexanedione and its retention time was used to detect the presence of this compound in other reaction mixtures. The relative amounts of the two major products were three to one.

Methyl p-toluenesulfonate Doubly recrystallized p-toluenesulfonic acid was dissolved in diethyl ether and allowed to react with a solution containing an excess of diazomethane in benzene. The ether and a portion of the benzene were removed by distillation and the remaining mixture was analysed on an Apiezon M column at 167° in the DHF gas chromatography instrument. The product from this reaction, methyl p-toluenesulfonate, was found to have a retention time dis-

tinctly longer than that for the n-butyl enol ether of 2,4-pentanedione. This retention time was utilized in identification of methyl p-toluenesulfonate in other reaction mixtures.

Apparatus

The kinetics of the reaction of diazomethane with 2,4-pentanedione were measured at 27.0 ± 0.03°. The constant temperature water bath which was maintained at this temperature was controlled by a Labline Differential Type Rota-Set Regulator No. 3202 which was actuated by a Fisher Electronic Relay No. 13-001. A constant head device for supplying cooling water for the bath through an inlet controlled by a needle valve was not used except when hot weather placed great stress on the regulator and relay.

Potentiometric titrations were carried out using a Beckman pH meter, Model G, which was carefully grounded. The electrodes were a Beckman general purpose glass electrode (No. 1190-80), and a Beckman sleeve type Calomel reference electrode (No. 1170-71). The Calomel electrode was modified for titrations in non-aqueous media by replacing the aqueous potassium chloride solution with a saturated solution of potassium chloride in methanol.

Titration cells consisted of 200 ml. tall-form lipless beakers. A round piece of composition material with holes drilled to hold the two electrodes, the burette tip, and nitrogen inlet tube was fastened to the beaker with two pieces of

rubber electrical tape. Mixtures were stirred during the titrations by a magnetic stirrer and polyethylene-covered stirring bars. The stirrer was grounded but upon use for a long period of time the stirrer heated up considerably and thereby caused erratic behaviour in the pH meter. This difficulty was circumvented by placing a crystallizing dish of water on the stirrer and placing the titration cell in the dish.

Normax ten milliliter burettes, graduated in five hundredths, were used. A five milliliter microburette was also used. Teflon stop-plugs replaced the usual glass stop-plugs.

All titrations were carried out under a slow stream of dry nitrogen. Tetra-alkylammonium hydroxide in benzene - methanol was stored in a blackened two-liter bottle connected to a lecture bottle of prepurified nitrogen and was siphoned out under pressure of this nitrogen.

Gas-liquid-partition-chromatography Two instruments were used in this work. One was a commercial unit; a Consolidated Electrodynamics Corporation Type 26 - 201 Chromatograph Analyser. This instrument was made available through the courtesy of Professor A. F. Voigt and his group. Metal columns supplied with the instrument were replaced by glass columns. This instrument is designated as the CEC instrument throughout this thesis. The other instrument, designated as the DHF instrument, was constructed by Donald H. Froemsdorf and utilizes a Gow-Mac pretzel type conductivity cell.

The Apiezon M column for the CEC instrument was a nine foot, glass coiled column packed with 17 parts of Apiezon M on 43 parts (by weight) fire-brick (40-60 mesh).

The Apiezon L column for the DHF instrument was a fifteen foot, coiled copper tube packed with 10 parts (by weight) of Apiezon L on 30 parts of fire-brick (40-60 mesh).

The Apiezon M column for the DHF instrument was a fifteen foot, coiled copper tube packed with 33 parts Apiezon M (by weight) on 83 parts of fire-brick.

Distillation column The distillations in this work, both at reduced pressure and at atmospheric pressure, were done using a spiral tantalum wire column, 74 centimeters long and 7 millimeters in diameter, which was constructed by Richard Schwendiger. A spinning band column proved unsatisfactory for distillations of 2,4-pentanedione since the compound reacted with the metal in the wire to form a metal chelate.

Rate measurements

Determination of diazomethane The concentration of diazomethane in all solutions analysed, reaction mixtures and otherwise, was determined indirectly by adding an aliquot of the solution being analysed to a known excess of salicylic acid (an appropriate aliquot of a solution in 1,2-dimethoxyethane). The diazomethane reacts immediately (within several minutes). Consequently, in the analysis of reaction mixtures, addition to the salicylic acid quenches the reaction. Unreacted salicylic

acid was back-titrated potentiometrically in acetone with 0.1 molar triethyl-n-butylammonium hydroxide. In any solution containing 2,4-pentanedione the change in potential at the end-point is decreased considerably. Sufficient data have been collected to indicate that phenol red could be used for the indicator in the analysis of solutions not containing 2,4-pentanedione. It changes color within 0.03 milliliters after the stoichiometric end-point. In solutions containing 2,4-pentanedione, bromcresol purple might be a reliable indicator. Data accumulated in a couple of runs (one of these also contained p-toluenesulfonic acid) seemed to indicate that bromcresol purple changed color within 0.03 milliliters prior to the end-point.

It is interesting to note that p-toluenesulfonic acid could not be used to analyse for concentrations of diazomethane. The reaction was complete in a minute or so, but was not quantitative in terms of acid consumed. About 10% less acid, in terms of moles, reacted than diazomethane (based on comparison with analysis of the same solution with salicylic acid). Use of p-toluenesulfonic acid as a method of analysis would lead to low values for diazomethane concentration.

Determination of 2,4-pentanedione In analysis of reaction mixtures of diazomethane and 2,4-pentanedione for the diketone, an aliquot of the mixture was added to a known excess (just sufficient to quench the reaction) of salicylic acid solution. The 2,4-pentanedione concentration was then deter-

mined by potentiometric titration in pyridine with triethyl-n-butylammonium hydroxide. Two breaks are observed. The first corresponded to the unreacted salicylic acid present, and the second corresponded to the amount of methyl salicylate (product of the reaction of diazomethane with salicylic acid) and 2,4-pentanedione present. In solutions containing methyl p-toluenesulfonate this material was also titrated along with the methyl salicylate and the 2,4-pentanedione. The stoichiometry of the titration of methyl p-toluenesulfonate was not checked directly. This will be discussed in more detail in the cases where consideration of this factor is applicable.

The 2,4-pentanedione determination is of low accuracy because it depends on taking the difference between two breaks and because this difference is made up of contributions from more than one species (i.e., 2,4-pentanedione, methyl salicylate, and, sometimes, methyl p-toluenesulfonate). Furthermore, the break is small and occurs over a range of two to three tenths of a milliliter. That the break is detectable at all can be attributed to the existence of a flat portion of the titration curve prior to the break.

Determination of p-toluenesulfonic acid In analysis of solutions for the concentration of p-toluenesulfonic acid present, an aliquot (quenched in salicylic acid solution if diazomethane was present) was titrated potentiometrically in acetone with methanolic sodium hydroxide. The break is large, hence it should be possible to find an indicator whose color

change would correspond to the break in potential. No indicator, of those tried, would do this.

General procedure Reaction and control mixtures were prepared from stock solutions previously equilibrated at 27.0°. In a typical run, 10 milliliters of 2,4-pentanedione were mixed with a 90 milliliter aliquot from a stock solution of p-toluenesulfonic acid in 1,2-dimethoxyethane in a 200 milliliter volumetric flask. The reaction was commenced by the addition of 100 milliliters of diazomethane in benzene. Aliquots were withdrawn at intervals from the reaction mixtures for analysis. The first sample was titrated with methanolic sodium hydroxide to determine the concentration of unreacted p-toluenesulfonic acid. Then alternate samples were used for the determination of diazomethane and 2,4-pentanedione. The control solutions were also sampled and analysed for diazomethane at intervals. Titrants and salicylic acid stock solution were standardized both immediately before and after the run.

Initial concentrations of 2,4-pentanedione and p-toluenesulfonic acid were determined by analysis of a blank solution identical with the reaction mixture, but with diazomethane absent. The initial concentration of diazomethane was estimated from the rates of decomposition of two control solutions and the diazomethane stock solution.

Reactions in benzene The rates of two reactions of diazomethane with 2,4-pentanedione in benzene solution were followed. The two reactions varied in that the 2,4-pentane-

dione concentration of one was double that in the other. In one reaction the initial diazomethane concentration was 0.248 molar, and the initial 2,4-pentanedione concentration was 0.473 molar. In the other reaction, the solution was initially 0.300 molar in diazomethane and 0.975 molar in 2,4-pentanedione. The data are tabulated in Table 1 and Table 2.

Table 1. Reaction in benzene at 27.0°. 0.248 molar diazomethane and 0.473 molar 2,4-pentanedione

Time in minutes	(CH_2N_2), moles per liter in reaction mixture[a]	(CH_2N_2), moles per liter in blank mixture[b]
0	(0.248)	---
2	0.245	0.248
35	0.242	0.248
121	0.232	0.248
136	0.229	0.247
229	0.218	0.246
344	0.208	0.245
626	0.180	0.244
873	0.159	0.242
1235	0.136	0.238
1447	0.125	0.235
1714	0.110	0.234
2471	0.082	0.230
2784	0.080	0.226
3188	0.073	0.221
3946	0.066	0.211

[a]Experimentally determined

[b]Taken from a plot of (CH_2N_2) versus time for a solution identical to the reaction mixture but containing no 2,4-pentanedione

$$10^3 \times k = 1.29 \pm 0.28 \text{ liters per mole minute}$$

Table 2. Reaction in benzene at 27.0°. 0.300 molar diazomethane and 0.975 molar 2,4-pentanedione

Time in minutes	(CH_2N_2), moles per liter in reaction mixture[a]	(CH_2N_2), moles per liter in blank mixture[b]
0	(0.300)	---
2	0.299	0.295
47	0.283	0.293
74	0.274	0.292
205	0.231	0.288
236	0.221	0.287
362	0.185	0.283
510	0.146	0.277
532	0.140	0.276
589	0.119	0.273
678	0.120	0.273
726	0.108	0.273
1362	0.043	0.275

[a]Experimental values

[b]Taken from a plot of (CH_2N_2) versus time for a solution identical to the reaction mixture but containing no 2,4-pentanedione

$$10^3 \times k = 1.34 \pm 0.38 \text{ liters per mole minute}$$

The rate constants were determined for pairs of values of time and diazomethane concentration using the integrated form of the rate law, $dx/dt = k(a-y)(b-x)$, where the assumption is made that $y = cx$. The quantity c is evaluated from two expressions, $y = x + s$ and $y = cx$. The quantity y represents the amount of diazomethane (in moles per liter) reacted during a given time interval. The concentration-time behaviour of a mixture containing only diazomethane (no 2,4-pentanedione)

gives a measure of s, the amount of diazomethane consumed during the same time interval by decomposition independent of the diketone. The quantities y and x were used to obtain a c for every pair of values. An average c (1.12 and 1.15) was used in calculation of the rate constant, k. It is seen that in the rate law used, (a-y) represents the instantaneous diazomethane concentration (moles per liter) and (b-x) represents the instantaneous 2,4-pentanedione concentration. Each (a-y) is an experimentally obtained quantity. The values for (b-x) are calculated utilizing just one experimentally determined 2,4-pentanedione concentration, the initial concentration. The integrated form of the rate law used is given in Equation (1).

$$(1) \qquad \log \frac{(b-x)}{(a-y)} = \frac{cb-a}{2.303} kt + \log \frac{b}{a}$$

Reactions in diethyl ether-benzene The rate of the uncatalysed (spontaneous) decomposition of diazomethane in diethyl ether-benzene was followed. A benzene solution of diazomethane (100 milliliters) was added to an equal volume of diethyl ether (100 milliliters) to commence the reaction. Diazomethane concentrations were determined by analysis of five milliliter aliquots of the reaction mixture in the manner described previously. The initial diazomethane concentration, 0.290 molar, was estimated by extrapolation to zero time. The data are tabulated in Table 3.

In one experiment, the rate of change of diazomethane concentration in the presence of p-toluenesulfonic acid was

Table 3. Reaction in diethyl ether-benzene at 27.0°. 0.290 molar diazomethane

Time in minutes	Diazomethane concentration (moles per liter)
0	(0.290)
4	0.289
21	0.288
61	0.286
79	0.286
108	0.284
608	0.280
1320	0.273
3220	0.263

studied in the solvent system diethyl ether-benzene for a period of about three hours. A solution of p-toluenesulfonic acid in diethyl ether (50 milliliters) was mixed at zero time with a solution of diazomethane in benzene (50 milliliters). The reaction mixture was initially 0.038 molar in p-toluenesulfonic acid and 0.210 molar in diazomethane. The diazomethane concentration in two milliliter aliquots from the reaction mixture was determined as described previously. The concentration of diazomethane as a function of time is tabulated in Table 4. The concentration of p-toluenesulfonic acid during the course of the reaction was not measured.

In a similar experiment, a benzene solution of diazomethane (100 milliliters) was added to a solution of p-toluenesulfonic acid in diethyl ether (100 milliliters) to commence the reaction. The initial concentrations were: p-toluene-

Table 4. Reaction in diethyl ether-benzene at 27.0°. 0.210 molar diazomethane and 0.038 molar p-toluenesulfonic acid

Time in minutes	Diazomethane concentration (moles per liter)
0.00	(0.210)
1.75	0.167
5.0	0.176
28.0	0.153
39.1	0.144
51.9	0.139
69.8	0.136
81.8	0.131
94.0	0.129
107	0.128
120	0.127
132	0.127
142	0.128
152	0.132
161	0.128

sulfonic acid, 0.0874 molar; and diazomethane, 0.279 ± 3% molar. In addition to the usual analysis for the concentration of diazomethane (five milliliter aliquots), the reaction mixture was analysed for the amount of strong acid present. This was done by titrating a two milliliter aliquot of the reaction mixture (quenched with an ether solution of salicylic acid) with methanolic sodium hydroxide. No strong acid was found to be present, even in the first analysis at three minutes. The methanolic sodium hydroxide titration method was checked in independent experiments and found that it would easily detect an amount of p-toluenesulfonic acid (strong acid) equivalent to

5% of the amount present initially in the reaction mixture but would not detect an amount equivalent to 2% of the acid present initially. See Table 5.

Diazomethane concentration as a function of time was measured for a reaction mixture which contained diazomethane, 2,4-

Table 5. Reaction in diethyl ether-benzene at 27.0°. 0.279 ± 3% molar diazomethane and 0.0874 molar p-toluenesulfonic acid

Time in minutes	Diazomethane concentration (moles per liter)
0	(0.279)
3	0.180[a]
5	0.181
32	0.179[a]
40	0.178
66	0.177[a]
80	0.177
96	0.176[a]
119	0.174
133	0.175[a]
159	0.172[a]
171	0.172
194	0.170[a]
205	0.169
244	0.167
248	0.168[a]
330	0.163
344	0.163[a]
703	0.153
737	0.111[a]
914	0.148
1050	0.145
2680	0.136

[a]Two milliliter aliquot of reaction mixture; titrant was methanolic sodium hydroxide. Other values: five milliliter aliquot and tetralkylammonium hydroxide

pentanedione, and p-toluenesulfonic acid. The solvent was diethyl ether-benzene. In one experiment, a solution of p-toluenesulfonic acid and 2,4-pentanedione in diethyl ether (50 milliliters) was mixed with a solution of diazomethane in benzene (50 milliliters). The reaction mixture was initially 0.038 molar in p-toluenesulfonic acid, 0.210 molar in diazomethane, and 0.488 molar in 2,4-pentanedione. The data are tabulated in Table 6.

Table 6. Reaction in diethyl ether-benzene at 27.0°. 0.210 molar diazomethane, 0.038 molar p-toluenesulfonic acid, and 0.488 molar 2,4-pentanedione

Time in minutes	Diazomethane concentration (moles per liter)
0.00	(0.210)
2.5	0.165
8.3	0.164
17.1	0.165
41.5	0.157
50.0	0.156
60.9	0.153
73.7	0.150
85.8	0.148
97.3	0.148
108	0.146
121	0.142
133	0.140
145	0.138
157	0.133
173	0.127

In a similar experiment, the concentrations of all three components of the reaction mixture were measured as functions of time. A solution of diazomethane in benzene (100 milliliters) was added to a mixture of p-toluenesulfonic acid and 2,4-pentanedione in diethyl ether (100 milliliters) to commence the reaction. The initial concentrations were: p-toluenesulfonic acid, 0.0874 molar; diazomethane, 0.273 ± 3% molar; and 2,4-pentanedione, 0.499 molar. Once again it was observed that the sulfonic acid is consumed immediately upon mixing of the two solutions since no strong acid was detected in the first analysis, or thereafter. The concentration of diazomethane as a function of time is tabulated in Table 7. The time variation of 2,4-pentanedione concentration is given in Table 8. Included in Table 8, for comparison purposes, is the time-concentration data of a reaction system containing no sulfonic acid (benzene solvent). The 2,4-pentanedione concentrations in this case were calculated on the assumption of a 1:1 stoichiometry in the reaction of 2,4-pentanedione with diazomethane.

Reactions in 1,2-dimethoxyethane-benzene In order to reduce errors due to solvent volatility, further work was carried out using 1,2-dimethoxyethane in place of diethyl ether.

The rate of the uncatalysed decomposition of diazomethane in the solvent system, 1,2-dimethoxyethane-benzene, was measured at 27.0°. A solution of diazomethane in benzene (100 milliliters) was added to 1,2-dimethoxyethane (100 milliliters). Five milliliter aliquots from the reaction mixture were ana-

lysed for diazomethane as previously described. The concentration of diazomethane at zero time, 0.258 molar, was estimated from the rate of decomposition of the diazomethane stock solution. See Table 9.

Table 7. Reaction in diethyl ether-benzene at 27.0°. 0.273 ± 3% molar diazomethane; 0.0874 molar p-toluenesulfonic acid; and 0.499 molar 2,4-pentanedione

Time in minutes	Diazomethane concentration (moles per liter)
0	(0.273)
4	0.167[a]
7	0.166
40	0.158[a]
44	0.157
72	0.150[a]
76	0.148
106	0.140
112	0.139
144	0.133
188	0.126
218	0.119
278	0.110
283	0.108[a]
334	0.101
359	0.098
408	0.092
476	0.084
600	0.072
634	0.070
2210	0.014
2280	0.012
2330	0.013
2480	0.011[a]

[a]Determined with methanolic sodium hydroxide (two milliliter aliquot of reaction mixture)

Other values determined with triethyl-n-butyl ammonium hydroxide (five milliliters aliquot of reaction mixture).

Table 8. Reaction in diethyl ether-benzene at 27.0°. 0.273 ± 0.03% molar diazomethane; 0.499 molar 2,4-pentanedione; and 0.0874 molar p-toluenesulfonic acid

Time in minutes	2,4-Pentanedione concentration[a] (moles per liter)	Diazomethane[a] (moles per liter)
0	0.499	(0.273)
112	0.474	0.139
359	0.445	0.098
634	0.417	0.070
2330	0.394	0.013

[a]Determined experimentally

Reaction in benzene. 0.248 molar diazomethane; and 0.473 molar 2,4-pentanedione (see Table 1)

Time in minutes	2,4-Pentanedione concentration[b] (moles per liter)	Diazomethane[a] (moles per liter)
0	(0.473)	0.248
121	0.455	0.232
344	0.431	0.208
626	0.403	0.180
2470	0.305	0.082
3950	0.289	0.066

[a]Determined experimentally

[b]Calculated assuming that one molecule of 2,4-pentanedione reacts with one molecule of diazomethane

Table 9. Reaction in 1,2-dimethoxyethane-benzene at 27.0°. 0.258 molar diazomethane

Time in minutes	Diazomethane concentration (moles per liter)
0.00	(0.258)
2.78	0.255
29.3	0.253
59.0	0.253
84.7	0.252
250	0.249
354	0.247
441	0.245
508	0.243
637	0.241
755	0.240
895	0.235
1034	0.233

The rate of the acid-catalysed decomposition of diazomethane at 27.0° in the mixed solvent was determined. A solution of diazomethane in benzene (100 milliliters) was added to a solution of p-toluenesulfonic acid in 1,2-dimethoxyethane (100 milliliters). Diazomethane concentrations were determined in the usual manner. The initial concentration of diazomethane was 0.254 molar as estimated from concentration-time behaviour of the diazomethane stock solution and a blank mixture containing diazomethane but no p-toluenesulfonic acid. The initial p-toluenesulfonic acid concentration was 0.0938 molar as determined by titration of a blank solution containing p-toluene sulfonic acid but no diazomethane.

It was found that more base (triethyl-n-butylammonium

hydroxide) was required for neutralization (titration to the second break in pyridine) than could be accounted for by the quantities of salicylic acid and methyl salicylate present. This difference was attributed to reaction of the base with methyl p-toluenesulfonate. This difference is recorded as methyl p-toluenesulfonate concentration in Table 10.

Table 10. Reaction in 1,2-dimethoxyethane-benzene at 27.0°. 0.254 molar diazomethane and 0.0938 molar p-toluenesulfonic acid

Time in minutes	Diazomethane (moles per liter)	Methyl p-toluene-sulfonate (moles per liter)
0.00	(0.254)	0.000
4.28	0.139[b]	
9.25	0.142	
64.8	0.138	
128	0.137	
164	0.136	
258	0.135[a]	0.0436
326	0.133	
398	0.131	
434	0.130[a]	0.0575
526	0.127	
569	0.126[a]	0.0620
647	0.122	
683	0.122[a]	0.0620
818	0.114	
850	0.113[a]	0.0537
919	0.110	

[a]Two milliliter aliquot of reaction mixture. Titrant, triethyl-n-butyl ammonium hydroxide; titrating solvent, pyridine

[b]Titration of a five milliliter aliquot of reaction mixture. Titrant was methanolic sodium hydroxide; titrating solvent, acetone

After four minutes reaction time a five milliliter aliquot of the reaction mixture was titrated with methanolic sodium hydroxide and no strong acid (sulfonic acid) was detected. Although the titration curve indicated no contribution by strong acid, the difference in the diazomethane concentration at four minutes as determined from the methanolic sodium hydroxide titer and that at nine minutes might be attributed to a small amount of residual strong acid.

It would appear from this data that while essentially no p-toluenesulfonic acid remains in the reaction mixture after the first few minutes, still not all of it was converted to methyl p-toluenesulfonate. Thus, while the concentration of methyl p-toluenesulfonate never exceeded 0.062 molar as determined by titration, the initial concentration of p-toluenesulfonic acid was 0.0938 molar.

Concentrations of both diazomethane and 2,4-pentanedione were measured during the reaction in order to ascertain the stoichiometric relation between the two. A solution of diazomethane in benzene (100 milliliters) was added to a solution of 2,4-pentanedione in 1,2-dimethoxyethane. All solutions were at 27.0°. The initial diazomethane concentration, 0.265 molar, was estimated from the concentration-time behaviour of the stock solution of diazomethane and two blank solutions (identical with the reaction solution except that the diketone was absent). The initial 2,4-pentanedione concentration, 0.494 molar, was determined by titration of a blank solution (con-

taining no diazomethane). The data are summarized in Table 11.

Table 11. Reaction in 1,2-dimethoxyethane-benzene at 27.0°. 0.494 molar 2,4-pentanedione and 0.265 molar diazomethane

Time in minutes	Diazomethane (moles per liter)	2,4-Pentanedione (moles per liter)
0.00	(0.265)	(0.494)
2.27	0.260	
4.76	0.256	0.511
61.1	0.225	
138	0.191	0.453
147	0.189	
253	0.153	0.439
391	0.120	
424	0.112	0.392
487	0.101	
568	0.088	0.364
799	0.063	
858	0.056	0.324
861	0.057	
1009	0.043	0.316
1144	0.037	
1319	0.029	0.314
1322	0.028	
one week	0.000	0.284

Two graphs of this data were made. One was a plot of diazomethane concentration versus time. See Figure 1, page 38. The other was a plot of 2,4-pentanedione concentration versus time. See Figure 2, page 40. A smooth curve was drawn for each of these plots to represent the data in the best way. These smooth curves were used to obtain "corrected" values for diazomethane and 2,4-pentanedione concentrations. This cor-

Figure 1. Reaction of diazomethane and 2,4-pentanedione in 1,2-dimethoxyethane-benzene at 27.0°. Diazomethane concentration as a function of time

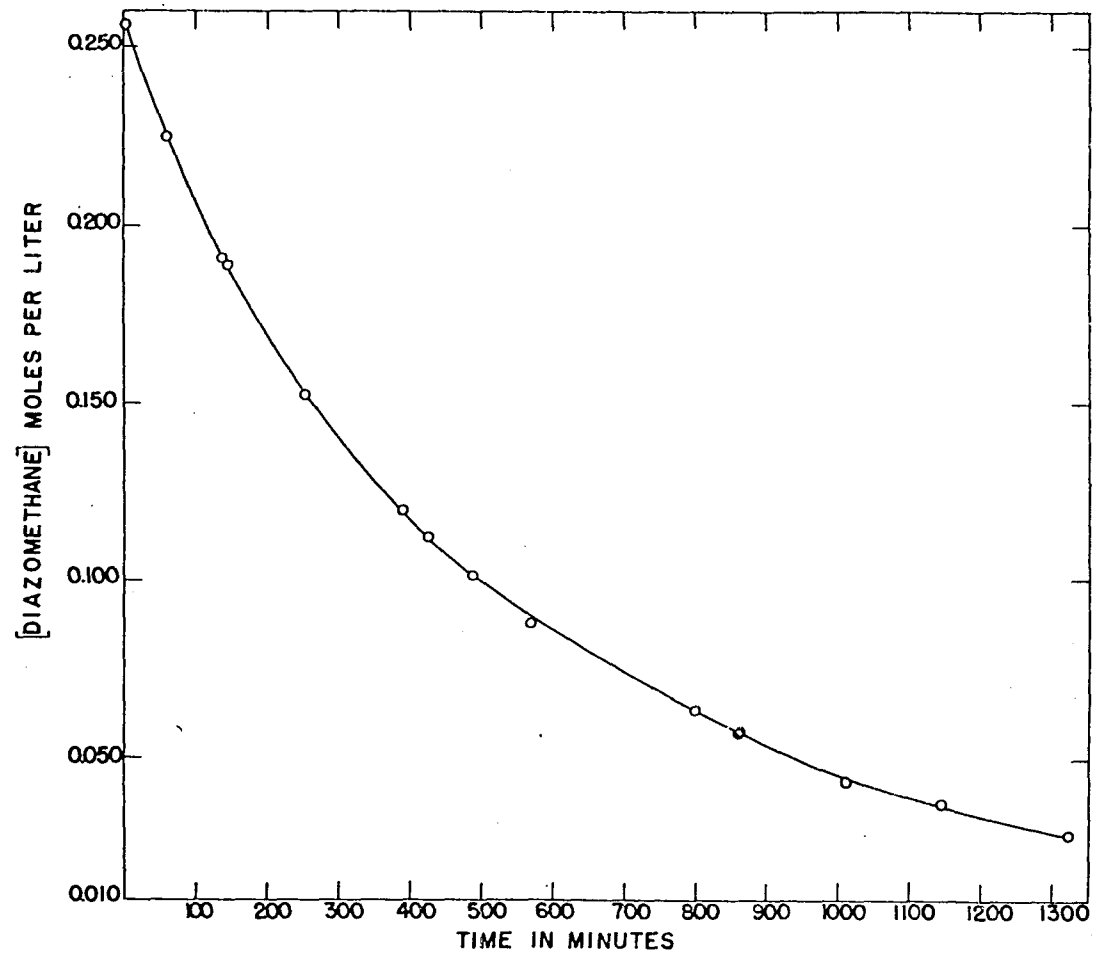
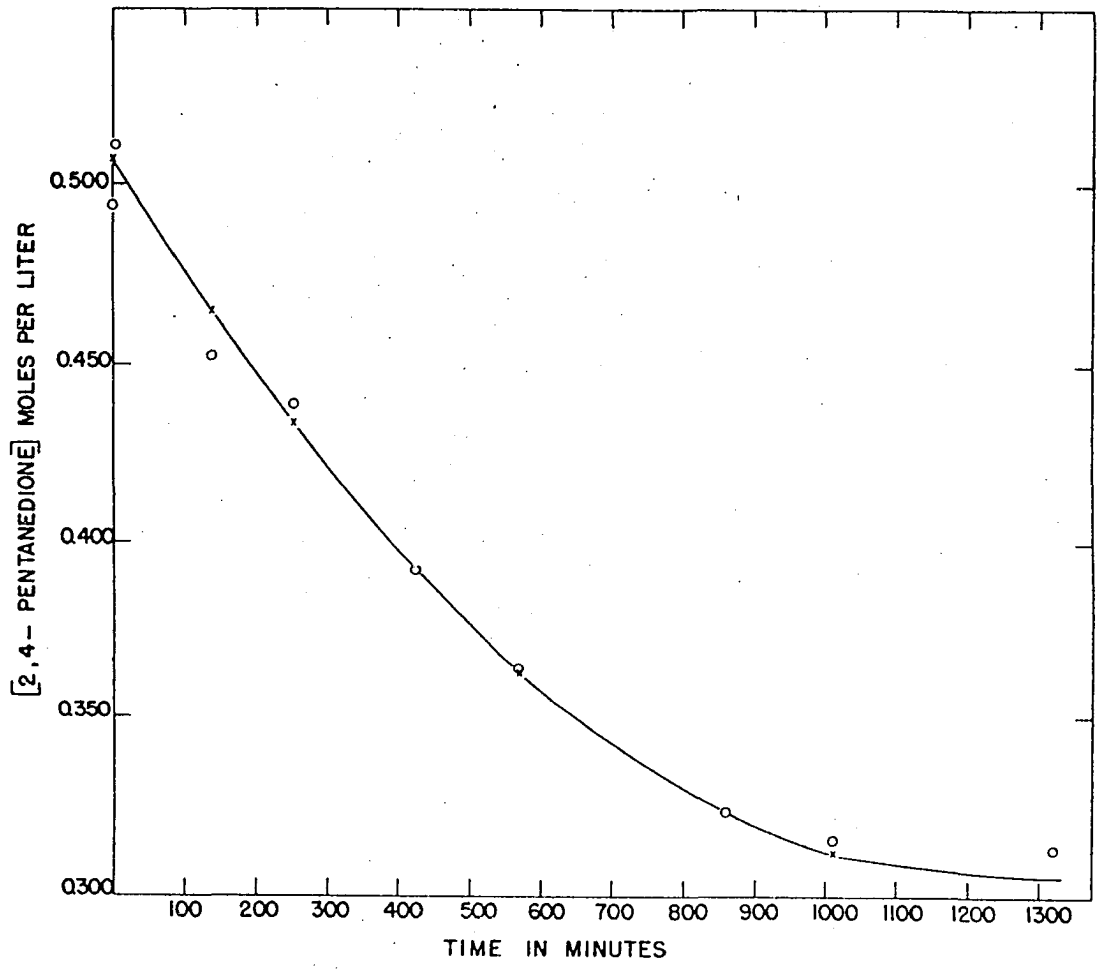

[DIAZOMETHANE] MOLES PER LITER
0.250
0.200
0.150
0.100
0.050
0.010
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
TIME IN MINUTES

Figure 2. Reaction of diazomethane and 2,4-pentanedione in 1,2-dimethoxyethane-benzene at 27.0°. Concentration of 2,4-pentanedione as a function of time. Experimental values are represented by O. Corrected values used in calculation of rate constants are represented by x.


[2,4- PENTANEDIONE] MOLES PER LITER
0.500
0.450
0.400
0.350
0.300
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
TIME IN MINUTES

rected data is tabulated in Table 12. The change in diazomethane concentration versus the change in 2,4-pentanedione concentration over the same time interval is plotted in Figure 6, page 63. The changes in concentrations were obtained from the data in Table 12. The line drawn at a forty-five degree angle to the abscissa represents 1:1 stoichiometry between diazomethane and 2,4-pentanedione.

Table 12. Reaction in 1,2-dimethoxyethane-benzene at 27.0°. 0.265 molar diazomethane and 0.494 molar 2,4-pentanedione

Time in minutes	Diazomethane[a] (moles per liter)	2,4-Pentanedione[b] (moles per liter)
050	0.229	0.492
100	0.207	0.476
200	0.169	0.448
300	0.141	0.421
400	0.117	0.397
500	0.099	0.376
600	0.086	0.357
700	0.074	0.343
800	0.063	0.331
900	0.053	0.320
1000	0.045	0.313
1100	0.039	0.309
1200	0.034	0.307
1300	0.029	0.306

[a]Values taken from curve. See Figure 1, page 38

[b]Values taken from curve. See Figure 2, page 40

Second order rate constants are calculated using Equation 2 as an approximation to the second order rate law.

$$(2) \quad \frac{\triangle(A)}{\triangle t (A)_{Av.} (D)_{Av.}} = k$$

$\triangle(A)$ = Change in concentration of the diketone over the time interval

$\triangle t$ = The time interval

$(A)_{Av.}$ = Average concentration of diketone during the interval

$(D)_{Av.}$ = Average concentration of diazomethane during the interval

Once again the concentrations of diazomethane and 2,4-pentanedione were taken from the curves depicted in Figures 1 and 2 (pages 38 and 40). The data used for the calculation of rate constants is found in Table 13. The average value of six rate constants so obtained was $4.35 \pm 0.80 \times 10^{-3}$ liters per mole minute.

With a strong acid initially present in the system, the concentrations of diazomethane and 2,4-pentanedione were measured at appropriate time intervals. It was desirable to note whether or not the relative rates of consumption of the two reactants were one to one. A solution of diazomethane in benzene (100 milliliters) was added to a solution of 2,4-pentanedione and p-toluenesulfonic acid in 1,2-dimethoxyethane (100 milliliters) to begin the reaction. Analyses were made as before. The first analysis was made using methanolic sodium hydroxide as titrant to detect the presence of strong acid. None was

Table 13. Data used for calculation of second order rate constants for the reaction of diazomethane with 2,4-pentanedione at 27.0°, in 1,2-dimethoxyethane-benzene

Time in minutes	2,4-Pentanedione[a] (moles per liter)	Diazomethane[b] (moles per liter)
0	0.5073	0.2653
138	0.4653	0.1910
253	0.4337	0.1530
424	0.3916	0.1120
568	0.3629	0.0898
858	0.3239	0.0572
1009	0.3124	0.0447

[a]Values taken from curve. See Figure 2, page 40

[b]Values taken from curve. See Figure 1, page 38

$$k = 4.35 \pm 0.80 \times 10^{-3} \text{ liters/mole minute}$$

found. The initial diazomethane concentration, 0.266 molar, was estimated as in the reaction mixture without sulfonic acid present. The initial concentration of 2,4-pentanedione, 0.247 molar, was determined by titration of a blank solution. The initial concentration of p-toluenesulfonic acid was 0.111 molar. The data are summarized in Table 14.

Two graphs of these data were made. One was a plot of diazomethane concentration versus time. See Figure 3, page 46. The other was a plot of 2,4-pentanedione concentration versus time. See Figure 4, page 48. A smooth surve was drawn for each of these plots to represent the data in the best manner.

Table 14. Reaction in 1,2-dimethoxyethane-benzene at 27.0°. 0.266 molar diazomethane; 0.247 molar 2,4-pentanedione; and 0.111 molar p-toluenesulfonic acid

Time in minutes	Diazomethane (moles per liter)	2,4-Pentanedione (moles per liter)
0.00	(0.266)	(0.247)
4.43	0.141	
8.51	0.140	
64.5	0.118	0.213
105	0.105	
200	0.081	0.166
227	0.077	
277	0.069	
308	0.065	0.157
355	0.059	
439	0.054	0.143
469	0.048	
564	0.042	0.142
595	0.037	
647	0.036	0.131
764	0.027	
825	0.027	0.128
13 days	0.005	0.122

These smoothed curves were used to furnish "corrected" values of diazomethane and 2,4-pentanedione concentrations. This corrected data is tabulated in Table 15. The change in diazomethane concentration for a given time interval versus the change in 2,4-pentanedione concentration over the same time interval is plotted in Figure 5, page 61. The changes in concentrations were obtained from the data in Table 15. The line drawn at a forty-five degree angle to the abscissa represents a consumption of one molecule of diazomethane for every one

Figure 3. Reaction of diazomethane, 2,4-pentanedione, and p-toluenesulfonic acid in 1,2-dimethoxyethane-benzene at 27.0°. Diazomethane concentration as a function of time. Experimental values are represented by 0. Corrected values used in calculation of rate constants are represented by x.

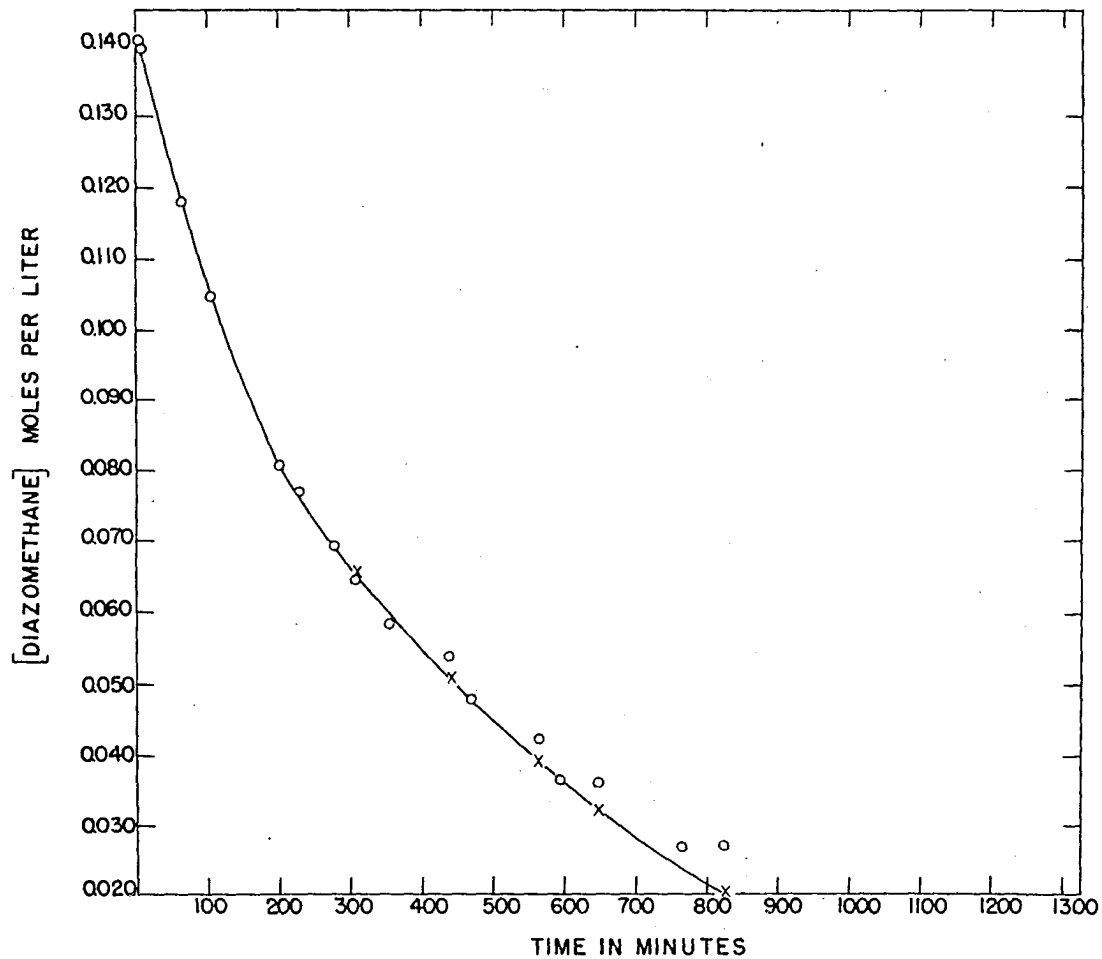

[DIAZOMETHANE] MOLES PER LITER
0.140
0.130
0.120
0.110
0.100
0.090
0.080
0.070
0.060
0.050
0.040
0.030
0.020
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
TIME IN MINUTES

Figure 4. Reaction of diazomethane, 2,4-pentanedione, and p-toluenesulfonic acid in 1,2-dimethoxyethane-benzene. 2,4-Pentanedione as a function of time. Experimental values are represented by O. Corrected values used in calculation of rate constants are represented by x.

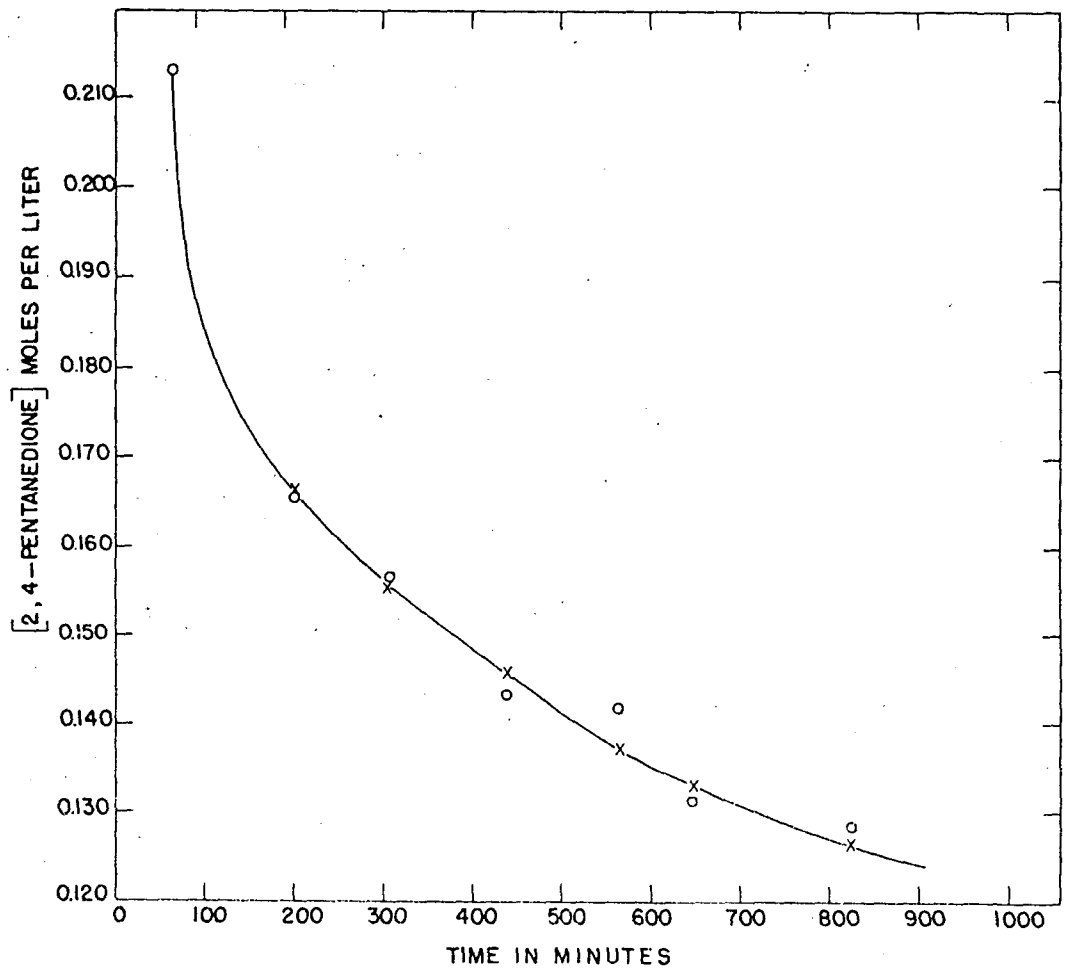

[2, 4-PENTANEDIONE] MOLES PER LITER
0.210
0.200
0.190
0.180
0.170
0.160
0.150
0.140
0.130
0.120
0
100
200
300
400
500
600
700
800
900
1000
TIME IN MINUTES

Table 15. Reaction in 1,2-dimethoxyethane-benzene at 27.0°. 0.266 molar diazomethane; 0.247 molar 2,4-pentanedione; and 0.111 molar p-toluenesulfonic acid

Time in minutes	Diazomethane[a] (moles per liter)	2,4-Pentanedione[b] (moles per liter)
050	0.123	---
100	0.106	0.184
200	0.081	0.166
300	0.067	0.156
400	0.055	0.148
500	0.045	0.141
600	0.036	0.135
700	0.028	0.131
800	0.020	0.127

[a]Values taken from curve. See Figure 3, page 46

[b]Values taken from curve. See Figure 4, page 48

molecule of 2,4-pentanedione reacted.

Second order rate constants were calculated in the same way as for the previous run with no strong acid present. Concentrations of diazomethane and 2,4-pentanedione were taken from the curves represented in Figures 3 and 4. The data used for calculating the rate constants are found in Table 16. The average value of six rate constants calculated in the previously described manner was $11.3 \pm 2.4 \times 10^{-3}$ liters per mole minute.

Table 16. Data used for calculation of second order rate constants for the reaction mixture of diazomethane, 2,4-pentanedione, and p-toluenesulfonic acid at 27.0° in 1,2-dimethoxyethane-benzene

Time in minutes	Diazomethane[a] (moles per liter)	2,4-Pentanedione[b] (moles per liter)
64.5	0.1180	0.2133
199.7	0.0808	0.1664
307.6	0.0654	0.1557
438.5	0.0508	0.1455
564.1	0.0392	0.1372
646.6	0.0323	0.1328
824.5	0.0200	0.1264

[a]Values taken from curve. See Figure 3, page 46

[b]Values taken from curve. See Figure 4, page 48

$k = 11.3 \pm 2.4 \times 10^{-3}$ liters/mole minutes

Determination of products

Diazomethane - 2,4-pentanedione in diethyl ether A reaction mixture in diethyl ether of diazomethane and 2,4-pentanedione (approximately equimolar quantities of the reactants) was subjected to analysis by gas-liquid-partition-chromatography. The mixture was also fractionated by distillation through a tantalum spiral wire distillation column, and the various fractions were analysed by gas chromatography. A chromatogram of the unfractionated reaction mixture indicated two major peaks and several very minor peaks. One fraction from the distillation was unreacted 2,4-pentanedione. The

other fraction, boiling 61-62° at 10-11 mm., contained the product, the methyl enol ether of 2,4-pentanedione (4 methoxy-3-pentene-2-one). In both of these fractions, gas chromatograms gave evidence for the presence of another component. This product corresponded to one of the minor peaks (occurring after the 2,4-pentanedione peak but before the methyl enol ether peak) in the chromatogram of the unfractionated reaction solution. It was identified as 3-methyl-2,4-pentanedione on the basis of correspondence of peak position (retention time) in the gas chromatographic analysis with that for authentic 3-methyl-2,4-pentanedione. These results were obtained using both an Apiezon L column in the DHF instrument and an Apiezon M column in the CEC instrument.

Two very minor peaks (occurring just after the methyl enol ether peak) seemed to be characteristic of the diazomethane - 2,4-pentanedione reaction mixture since they appeared in all analyses. One could possibly be assigned as being due to the ethyl enol ether but the exact correspondence of peak position with that of the calibration compound could not be established with certainty.

Two reaction mixtures in which diazomethane was present in about two-fold excess were analysed in a similar manner. The gas chromatogram showed the 2,4-pentanedione peak, the 3-methyl-2,4-pentanedione peak, the methyl enol ether peak, and the trace double peak (in that order) as in the above reaction

mixture, but there were two additional minor peaks which were not characterized. One occurred just before the 2,4-pentanedione peak and the other occurred just after it.

Homologous aklyl enol ethers To complement the kinetic analyses of the diazomethane - 2,4-pentanedione reaction, with and without p-toluenesulfonic acid, in 1,2-dimethoxyethane - benzene product determinations were made. Specifically, it was of importance to note whether or not the products in the p-toluenesulfonic acid catalysed reaction were different from those formed in the uncatalysed reaction. The retention times for ethyl and n-butyl enol ethers of the diketones were measured and used to determine the presence of these compounds in the reaction mixtures of diazomethane. The gas-liquid-partition-chromatographic analyses for this particular phase of the work and for all work discussed henceforth were performed utilizing the fifteen foot Apiezon M column in the DHF instrument at 167°.

Diazomethane - 2,4-pentanedione The reaction mixture analysed by gas chromatography was formed from a solution 0.25 molar in diazomethane and 0.48 molar in 2,4-pentanedione in 1,2-dimethoxyethane - benzene at 27.0°. The gas chromatogram showed a peak for 2,4-pentanedione, a minor peak for 3-methyl-2,4-pentanedione, a major peak for the methyl enol ether, and a very minor double peak in that order. This agrees with the analyses of the reaction in diethyl ether. Very little poly-

methylene was formed.

Diazomethane - 2,4-pentanedione - p-toluenesulfonic acid

The reaction in 1,2-dimethoxyethane - benzene at 27.0° of 0.20 molar diazomethane, 0.48 molar 2,4-pentanedione, and 0.11 molar p-toluenesulfonic acid was carried out and analyses by GLPC were made. The peaks of the chromatogram, in order of their appearance, were 2,4-pentanedione, 3-methyl-2,4-pentanedione (about five percent of the product formed), a peak which could be assigned as due to 2,4-hexanedione (3%), the methyl enol ether peak (92%), and the doublet peak, part of which might be due to the ethyl enol ether (1/2%). This analysis was made on filtered and concentrated (removal of some solvent in vacuo) reaction mixture. Unfiltered reaction mixture gave an additional low, broad peak with a retention time greater than that of the ethyl enol ether, and not as great as that of n-butyl enol ether. This peak was not identified. A similar peak is observed in the reaction product from diazomethane and p-toluenesulfonic acid in the absence of 2,4-pentanedione. Its position, however, does not coincide with that from the 2,4-pentanedione reaction. In any case, there was no evidence for the presence of the ethyl or n-butyl enol ethers in this reaction mixture. One analysis showed a component with a long retention time. The peak position corresponded to that for methyl-p-toluenesulfonate. A considerable amount of polymethylene was formed.

Diazomethane - p-toluenesulfonic acid A reaction mixture in 1,2-dimethoxyethane - benzene containing 0.20 molar diazomethane and 0.11 molar p-toluenesulfonic acid was allowed to react at 27.0° and analysed by gas chromatography. The chromatogram showed two quite small peaks and a low, broad peak with a higher retention time. One of the small peaks coincided in retention time with 2,4-hexanedione so that some question remains as to the actual existence of 2,4-pentanedione among the diazomethane - 2,4-pentanedione - p-toluenesulfonic acid reaction products. The broad peak, which did not coincide in position with that observed in the diazomethane - 2,4-pentanedione - p-toluenesulfonic acid reaction mixture was not identified. A considerable amount of polymethylene was formed.

Reaction in high concentrations of 2,4-pentanedione Reaction mixtures prepared from equal volumes of 2,4-pentanedione and 0.5 molar diazomethane in solvent (benzene or 1,2-dimethoxyethane) were studied. Reaction mixtures prepared in the same way except for the inclusion of p-toluenesulfonic acid were also studied.

In benzene, the reaction of 2,4-pentanedione (5.0 molar) with diazomethane (0.25 molar) was fairly rapid, but nitrogen evolution was still observable after four hours. There was no polymethylene visible. Product analysis by GLPC showed that ethyl or n-butyl enol ethers were not present.

A similar reaction mixture, but including p-toluene-

sulfonic acid (0.1 molar), gave a vigorous reaction and nitrogen evolution was complete within one and a half hours. No polymethylene was formed. Again no ethyl or n-butyl enol ethers were found in the reaction mixture.

In 1,2-dimethoxyethane, the reaction of 2,4-pentanedione (5 molar) with diazomethane (0.25 molar) was fast, the yellow diazomethane color being gone at the end of three hours. A very slight amount of polymethylene was observed. The gas chromatogram for this mixture showed, in order, the 2,4-pentanedione peak, the two peaks which might be attributed to 3-methyl-2,4-pentanedione and to 2,4-hexanedione, the methyl enol ether peak, and a small peak further out which did not correspond to ethyl enol ether.

In 1,2-dimethoxyethane, reaction of a mixture containing 2,4-pentanedione (5 molar), diazomethane (0.25 molar), and p-toluenesulfonic acid (0.1 molar) was so vigorous that the system had to be cooled with cold water before all the diazomethane solution could be added. Reaction was complete in one hour. A very slight amount of polymethylene was observed. The product composition was similar to that for the reaction in 1,2-dimethoxyethane with the sulfonic acid absent. One other component was observed, and its retention time corresponded to the unidentified peak found in the spectrum of the products from the reaction mixture of p-toluenesulfonic acid, 2,4-pentanedione and diazomethane (page 53). The product com-

position for the reaction with a high concentration of 2,4-pentanedione is qualitatively similar to that for the reaction at low concentration of 2,4-pentanedione. The amount of methyl enol ether formed appears to be decreased in comparison to the yields in reactions with lower concentrations of diketone or in the absence of acid.

Boron trifluoride - 2,4-pentanedione - diazomethane A reaction mixture was made up which was 0.24 molar in diazomethane, 0.63 molar in 2,4-pentanedione, and 0.13 molar in strong acid. The strong acid was hydrofluoric acid - hydrofluoboric acid generated from the reaction of 2,4-pentanedione with boron trifluoride to form difluoroboron acetylacetonate (25). The 2,4-pentanedione solution in 1,2-dimethoxyethane containing the strong acid and difluoroboron acetylacetonate had already started to decompose and was a rather deep yellow by the time the diazomethane in benzene was added. The reaction was violent. Copious quantities of polymethylene were formed. The reaction was over immediately, considerable heat and nitrogen being evolved. Cooling was necessary. The gas chromatographic analysis for this mixture showed, in order, the 2,4-pentanedione peak, a new large peak which was also present in the analysis of the boron trifluoride - 2,4-pentanedione solution containing no diazomethane, the methyl enol ether peak, a peak nearly as large as the methyl enol ether peak which could well have been due to ethyl enol ether, and a small peak at high retention time but which was not due to the

n-butyl enol ether.

The reaction was run again, this time adding the diazomethane solution just as a slight yellow tinge started to form in the boron trifluoride - 2,4-pentanedione solution. The concentrations were: 0.44 molar 2,4-pentanedione; 0.2 molar diazomethane; and 0.12 molar strong acid. The GLPC analysis was similar to that for the first reaction except that no peak which could be assigned to the ethyl enol ether was found.

Two other qualitative observations are worthy of note. During the preparation of one solution of 2,4-pentanedione - difluoroboron acetylacetonate, so much boron trifluoride was passed into the solution that two layers formed. The top layer behaved as the previously prepared solutions when diazomethane was added to it. When the bottom layer, which contained a very high concentration of acid, was allowed to react with diazomethane, no polymethylene was formed.

The other observation concerns the reactivity of a solution of impure difluoroboron acetylacetonate, 2,4-pentanedione, and diazomethane in 1,2-dimethoxyethane. Some of the acetonate was prepared in diethyl ether and isolated. The solid product was subjected to a crude recrystallization and then incorporated into the reaction system. Reaction was extremely vigorous. Much polymethylene was formed. Heat and nitrogen were evolved.

Discussion

Solutions of diazomethane in inert solvents (e.g., benzene, ether) are not stable. The concentration of diazomethane decreases slowly over a period of time, the process of decomposition being accelerated by rough surfaces, sources of proton, and light. The principal product of this spontaneous decomposition is polymethylene, $--(CH_2)_n--$. Introduction of p-toluenesulfonic acid, a proton source, into a solution of diazomethane leads to immediate reaction of the acid with diazomethane to yield methyl p-toluenesulfonate. With an excess of p-toluenesulfonic acid, slightly less (ca. 10%) than a mole of acid is required to consume a mole of diazomethane. On the other hand, with diazomethane in excess, there is immediate reaction and acid cannot be detected (within the limits of the method of analysis) in the reaction medium. Yet diazomethane which remains in the solution after this initial reaction proceeds to decompose (by polymerization) somewhat more rapidly than diazomethane alone in solution.

In a diazomethane solution containing p-toluenesulfonic acid initially, then, as compared to a solution containing only diazomethane, either there is some new species present, or there is a species which is present in higher concentration. In the former category, a possibility is that methyl p-toluenesulfonate is reacting with diazomethane. Such a reaction might proceed as indicated in Equations 3.

(3) a. $CH_2N_2 + CH_3OSO_2C_7H_7 \longrightarrow ({}^{+}N_2CH_2CH_3{}^{-}OSO_2C_7H_7)$

b. $({}^{+}N_2CH_2CH_3{}^{-}OSO_2C_7H_7) \longrightarrow {}^{+}N_2CH_2CH_3 + {}^{-}OSO_2C_7H_7$

c. ${}^{+}N_2CH_2CH_3 + nCH_2N_2 \longrightarrow CH_3(CH_2)_nCH_2{}^{+}N_2 + N_2$

In the latter category, a possibility which is more likely is that protonated species ($HOSO_2C_7H_7$, solvated proton, or $H_3{}^{+}O$), are responsible for the increased decomposition. These species, although not present in quantities which can be detected by titration, are sufficiently plentiful to initiate and maintain an acid-catalysed polymerication of diazomethane. In such a process, protonation of diazomethane would give methyl diazonium ions (which might lose nitrogen, giving methyl cations as the reactive species). Methyl diazonium ions could react with diazomethane to form the next higher alkyl diazonium ion (or alkyl cation). This process would continue until transfer of a proton from a growing chain to diazomethane occurred, or until p-toluenesulfonate anions were alkylated by the chain. This scheme of reaction is set forth in Equations 4.

(4) a. $CH_2N_2 + {}^{+}H \longrightarrow CH_3{}^{+}N_2$

b. $CH_3{}^{+}N_2 + nCH_2N_2 \longrightarrow CH_3(CH_2)_n{}^{+}N_2 + nN_2$

c. $CH_3(CH_2)_n{}^{+}N_2 \longrightarrow CH_3(CH_2)_{n-2}CH = CH_2 + {}^{+}H + N_2$

d. $CH_3(CH_2)_n{}^{+}N_2 + H_2O \longrightarrow CH_3(CH_2)_nOH + {}^{+}H + N_2$

e. $CH_3(CH_2)_n{}^{+}N_2 + {}^{-}OSO_2C_7H_7 \longrightarrow CH_3(CH_2)_nOSO_2C_7H_7 + N_2$

The decomposition of diazomethane in solutions by itself prob-

ably would proceed in a similar way. The concentration of acid-catalyst, however, would be lower.

Thus, introduction of p-toluenesulfonic acid into a diazomethane solution is a way of generating a small, but significant concentration of alkyl diazonium ions (or alkyl cations) in solutions of diazomethane.

There are two effects of independently generated alkyl diazonium ions on the reaction of diazomethane with 2,4-pentanedione. First, the rate constant for the reaction has doubled (pages 42 and 49). Secondly, more diazomethane is reacting than is expected on the basis of a 1:1 stoichiometry for the reaction (Figure 5, page 61).

Not considering the results obtained in product analyses of diazomethane - 2,4-pentanedione reaction solutions for the moment, the doubling of the rate constant could be accounted for in terms of an increase in the importance of the reaction of 2,4-pentanedione in an acid-catalysed process involving alkyl diazonium ions. The importance of such an acid-catalysed reaction in the reaction mixture containing only 2,4-pentanedione and diazomethane cannot be determined merely from the change in rate encountered in going to a reaction mixture initially containing p-toluenesulfonic acid. More information in this regard is revealed in considering the stoichiometry of the 2,4-pentanedione - diazomethane reaction in the uncatalysed and in the acid-catalysed reaction mixtures.

That more than one molecule of diazomethane reacts for

each molecule of 2,4-pentanedione when p-toluenesulfonic acid is present initially indicates that diazomethane reacts with alkyl diazonium ions as well as with 2,4-pentanedione. That is, diazomethane is sufficiently nucleophilic to compete with 2,4-pentanedione for cationic species present, thus maintaining the polymerization reaction even in the presence of diketone.

The importance of the stoichiometry of the reaction of diazomethane with 2,4-pentanedione in the absence of p-toluenesulfonic acid now becomes apparent. For every molecule of 2,4-pentanedione that reacts, just one molecule of diazomethane reacts (Figure 6, page 63). Thus, in the reaction mixture of diazomethane and 2,4-pentanedione (no sulfonic acid), the concentration of alkyl diazonium ions must be quite low. Any appreciable amount of alkyl cations would react with diazomethane as well as with 2,4-pentanedione, leading to a ratio of diazomethane reacted to 2,4-pentanedione reacted which would be greater than one. The reaction of diazomethane with 2,4-pentanedione must not proceed to any significant extent by way of alkyl diazonium ions.

The argument, based on stoichiometry, that the reaction proceeds by direct reaction rather than by a mechanism involving free ions may be somewhat open to question. The argument does depend on measurements (2,4-pentanedione concentrations) in which experimental errors were fairly large.

More striking evidence for a mechanism not involving free

Figure 5. Reaction of diazomethane and 2,4-pentanedione, and p-toluene-sulfonic acid in 1,2-dimethoxyethane-benzene at 27.0°. Change in diazomethane concentration versus change in 2,4-pentanedione concentration. See page 44.

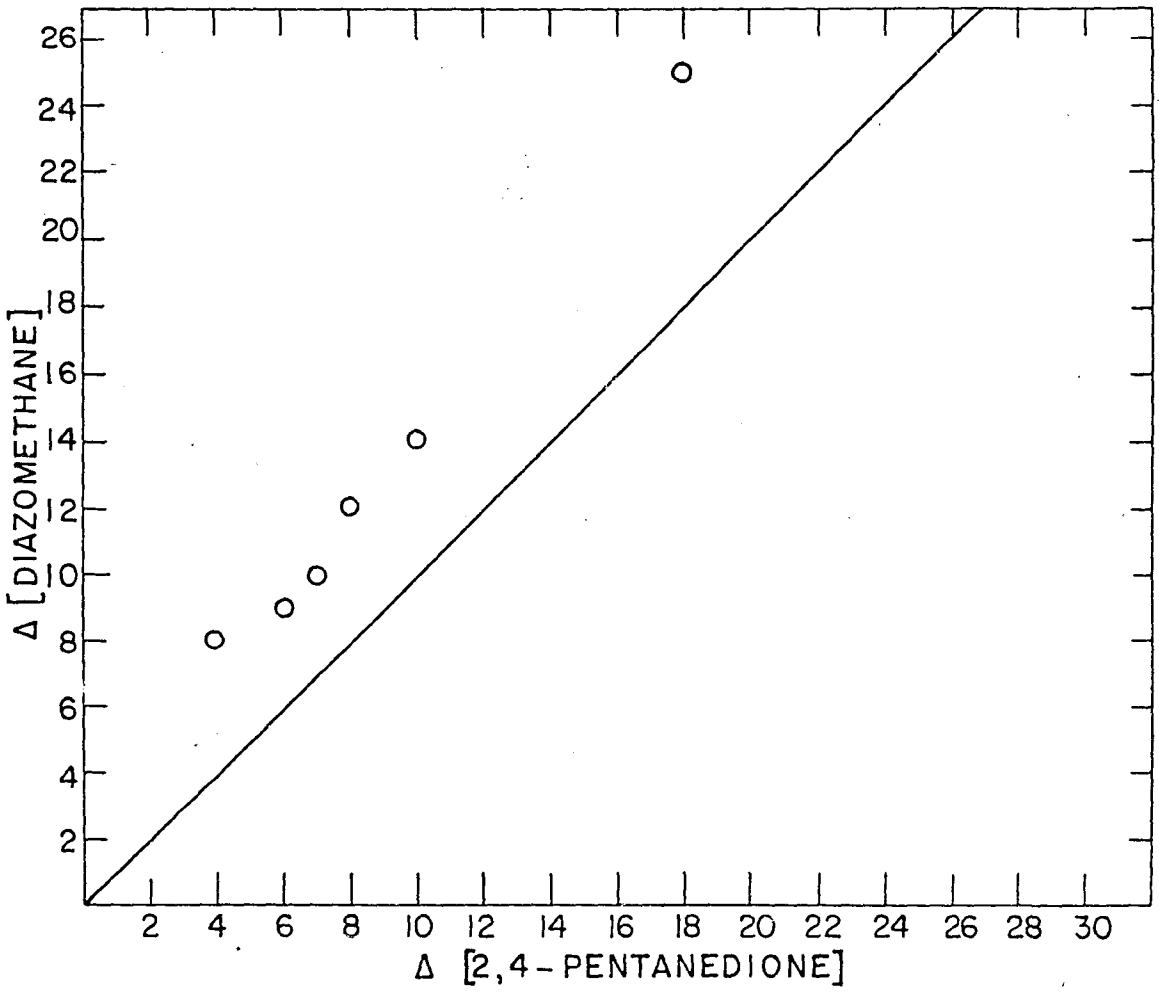
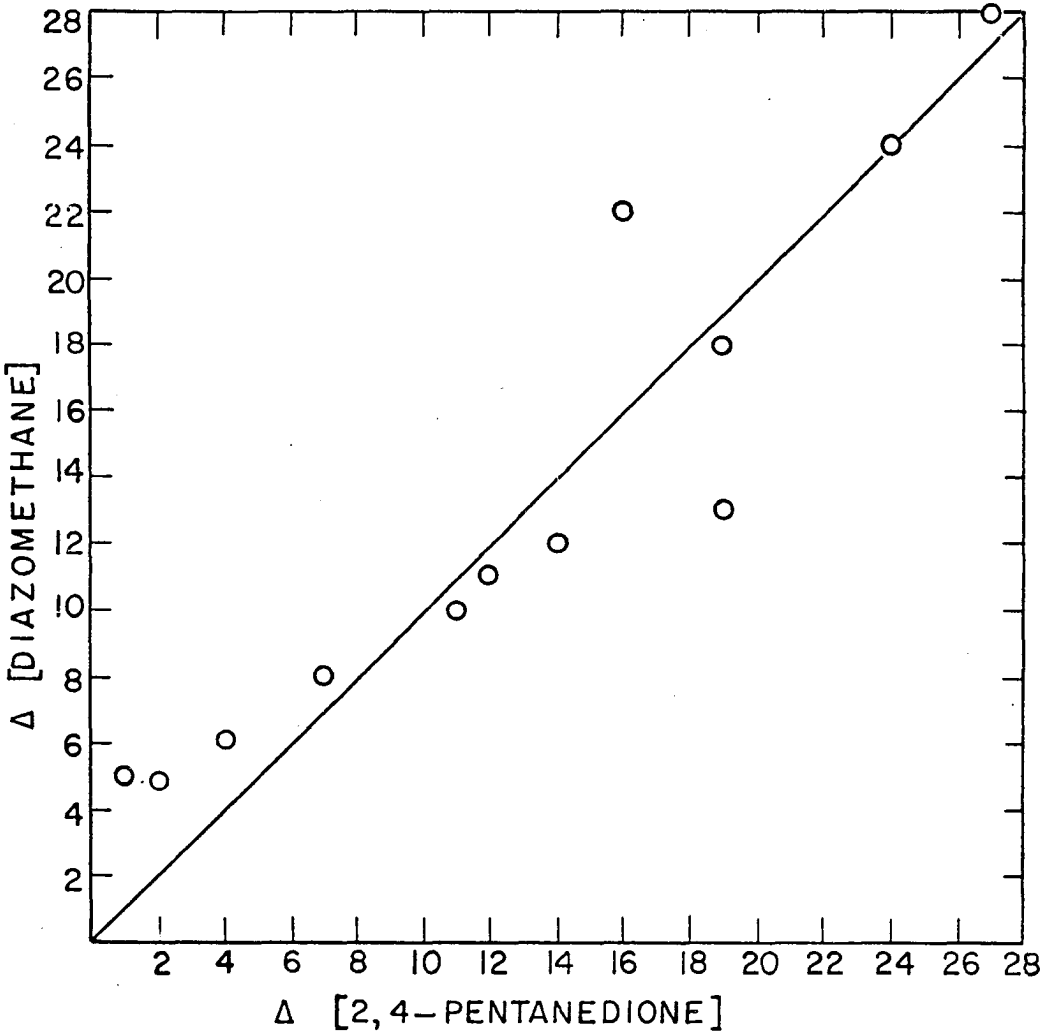

Δ [DIAZOMETHANE]
26
24
22
20
18
16
14
12
10
8
6
4
2
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Δ [2,4-PENTANEDIONE]

Figure 6. Reaction of diazomethane and 2,4-pentanedione in 1,2-dimethoxyethane-benzene at 27.0°. Change in diazomethane concentration versus change in 2,4-pentanedione concentration. See page 41.


Δ [DIAZOMETHANE]
Δ [2,4-PENTANEDIONE]
2
4
6
8
10
12
14
16
18
20
22
24
26
28

cationic species as intermediates is obtained from the analyses of products of the reactions. Neither reaction mixture contained any alkyl enol ether higher than methyl enol ether as indicated by absence, specifically, of ethyl and n-butyl enol ethers. Alkyl diazonium ions are being formed, in all probability, as is shown by the observation that more diazomethane is consumed than 2,4-pentanedione. Further indication of the presence of alkyl diazonium ions is that polymethylene is formed to a much greater extent in the reaction mixture of diazomethane and 2,4-pentanedione containing p-toluenesulfonic acid than in the reaction mixture not containing acid. Even in the presence of higher concentrations of alkyl diazonium ions, as generated by p-toluenesulfonic acid, 2,4-pentanedione does not react to form alkyl enol ethers other than methyl enol ether. Thus the formation of 4-methoxy-3-pentene-2-one (methyl enol ether of 2,4-pentanedione) in solutions not containing p-toluenesulfonic acid must occur in a concerted reaction between the reactants. On the other hand, it may proceed by way of ion pairs which collapse to form the methyl enol ether without diffusing apart.

Further evidence which is compatible with the one step mechanism are the studies in high concentrations of 2,4-pentanedione. In all systems studied, whether or not p-toluenesulfonic acid was present initially, the reaction of diazomethane with 2,4-pentanedione led only to the formation of the

methyl enol ether. No ethyl or n-butyl enol ethers were found in direct tests for their presence. Furthermore, polymethylene formation was negligible. One interpretation of these experiments is that 2,4-pentanedione, if present in sufficiently large amounts, can compete with diazomethane molecules for methyl diazonium ions. If so, the competition was sufficient in these experiments to prevent formation of higher alkyl diazonium ions almost completely. Another interpretation is that the direct reaction is speeded up to the extent that it is the only reaction of importance.

Only in the reaction of diazomethane with an aged solution of boron trifluoride - 2,4-pentanedione reaction products was there any evidence obtained for the formation of an alkyl enol ether of 2,4-pentanedione higher than methyl enol ether. The ethyl enol ether may well have been present, in sizeable amount, but no n-butyl enol ether was detected. The formation of ethyl enol ether might be explained by the fact that anions of the acid in this solution, BF_4^- and F^- ions, are less nucleophilic than p-toluenesulfonate anions. This would permit the formation of a higher concentration of alkyl diazonium ions, so that alkylation of 2,4-pentanedione by alkyldiazonium ions higher than the methyl begin to be of importance.

The results of product analyses indicate strongly the operation of a one step mechanism. However, the lack of formation of higher alkyl enol ethers in the p-toluenesulfonic

acid-catalysed reaction makes it difficult to account for the increased rate constant. Before the results of the product analyses were known, the doubling of the rate constant for the reaction in the presence of p-toluenesulfonic acid was accounted for in terms of additional consumption of 2,4-pentanedione by alkyl diazonium ions in the acid-catalysed reaction. Alkyl diazonium ions were considered not to be present in the reaction mixture containing only diazomethane and 2,4-pentanedione, in keeping with the product analyses and stoichiometry data.

Therefore, the doubling of the rate constant must be accounted for in some other way. Either a new reaction is also occurring which consumes 2,4-pentanedione, or an acid-catalysed reaction, not involving protonation of diazomethane, has become important. A possible reaction is alkylation of 2,4-pentanedione by methyl p-toluenesulfonate (and this might be acid-catalysed). Protonation of 2,4-pentanedione and reaction of the conjugate acid with diazomethane could also help account for the increase. Formation of 2,4-hexanedione is believed to occur in the reaction in the presence of p-toluenesulfonic acid, but not in the reaction with sulfonic acid absent. However, the product is not formed in sufficient amount to account for the doubling of the rate constant. It is possible that the unidentified compound (page 53) in the acid-catalysed reaction is formed in sufficient amounts to account for the

increase. But its presence was detected only in the unfiltered reaction mixture. This would indicate that it is probably a solid, and hence its total contribution to the product mixture might not be ascertained by the gas-liquid-partition-chromatographic analysis.

Summary

Evidence is presented which is compatible with a mechanism involving a direct, one step interaction between the reactants in the reaction of diazomethane with 2,4-pentanedione. The strongest piece of evidence is the fact that acid-catalysed polymerization of diazomethane occurs concurrently with the methylation of the diketone without any concomitant production of other enol ethers. Therefore, any mechanism proposed for the reaction of diazomethane with 2,4-pentanedione cannot involve the same intermediates (assumed to be alkyl diazonium ions) as are involved in the chain-propagation step of the polymerization reaction. Comparison of stoichiometry of the reaction in the presence and in the absence of p-toluenesulfonic acid initially lends support to the proposed mechanism for the reaction between diazomethane and 2,4-pentanedione. The stoichiometry in the absence of acid is one to one, but with p-toluenesulfonic acid present initially, more diazomethane than 2,4-pentanedione is consumed. In the presence of high concentrations of 2,4-pentanedione no polymethylene is formed indicating that, either the diketone competes so effectively with diazomethane for any methyl diazonium ions (methyl cations) that no polymer is formed, or that the direct reaction is now so fast that the polymerization reaction cannot survive.

A solution of boron trifluoride - 2,4-pentanedione reaction products react with diazomethane to produce a product

which might be ethyl enol ether. A possible explanation is advanced.

The rate constant for the reaction of diazomethane with 2,4-pentanedione and p-toluenesulfonic acid is double that for the reaction of diazomethane with 2,4-pentanedione alone. This fact, by itself, is compatible with a mechanism involving free cationic species, but the other data is not consistent with such a mechanism. Some explanations are suggested to account for the increase in rate.

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PART II. SYNTHESIS OF STERICALLY-HINDERED BETA-DIKETONES

Introduction

It was the purpose of this work to prepare two beta-diketones, $RCCH_2CR$ (with O above each C), with bulky alkyl (R) groups. One compound was 2,2,8,8-tetramethyl-4,6-nonanedione (I) which will be called bis-tertiarybutylacetylmethane in subsequent discussions.

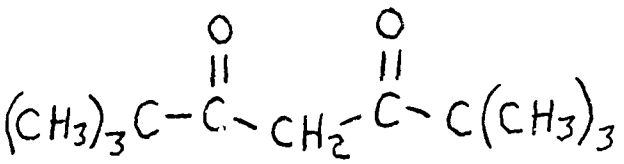
(I) $(CH_3)_3C-CH_2-C(=O)-CH_2-C(=O)-CH_2-C(CH_3)_3$

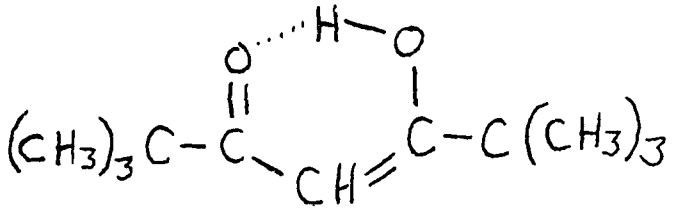
The other compound was 3,3,7,7-tetraethyl-4,6-nonanedione (II) which will be designated as bis-triethylacetylmethane in this discussion.

(II) $(CH_3CH_2)_3C-C(=O)-CH_2-C(=O)-C(CH_2CH_3)_3$

These two compounds are analogues of dipivaloylmethane (III), a sterically-hindered beta-diketone, studies of which have been

made by Guter (1), by Guter and Hammond (2), by Hammond and Fort (3), and by Hammond and Nonhebel (4). This compound exists almost entirely in the form of the symmetrical enolic modification (IV).

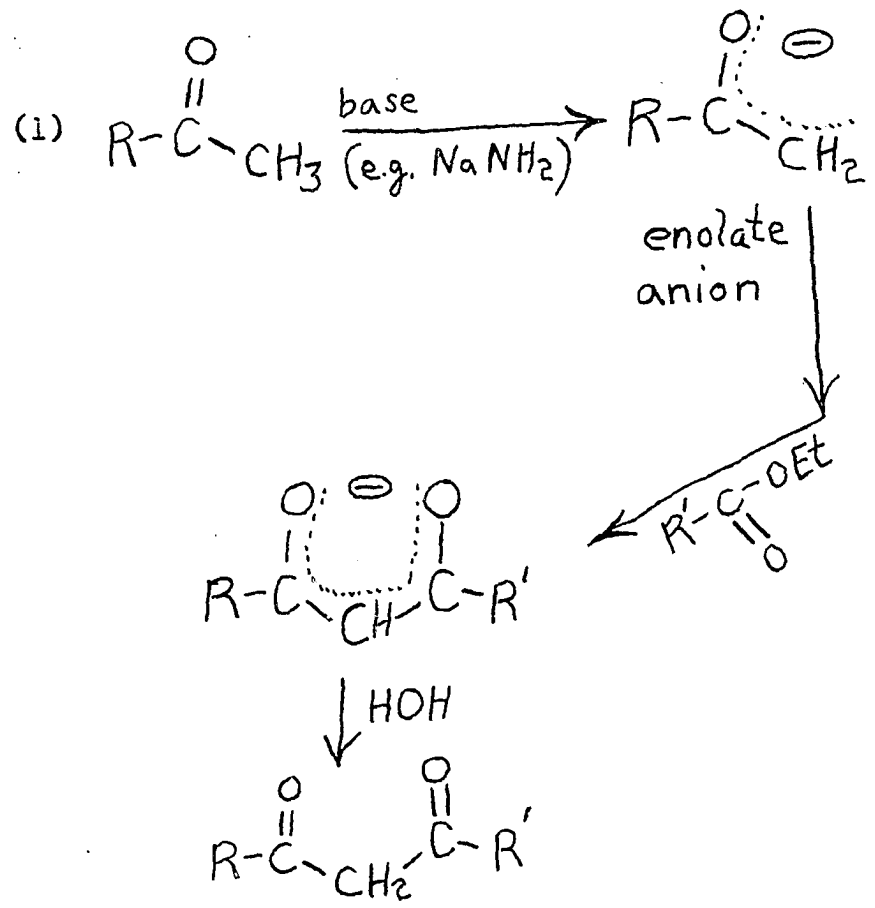
(III) 

(IV) 

Relative to dipivaloylmethane, bis-triethylacetylmethane is more sterically hindered, and bis-tertiarybutylacetylmethane is less so. These structural variations should lead to interesting variations in enolic content, acidity, formation constants of metal chelates, spectral and other physical properties, and chemical reactivity (in the diketones and their metal salts).

The final reaction in the preparation of these compounds is the condensation of the appropriate alkyl methyl ketone with an ester of the carboxylic acid whose alkyl group corresponds to that of the alkyl group in the ketone. (Obviously this method would apply to the preparation of unsymmetrical beta-diketones as well.) Consequently, much of this paper will deal with the preparation of the appropriate acids and ketones. The general scheme of reaction is presented in reaction sequence

(1):



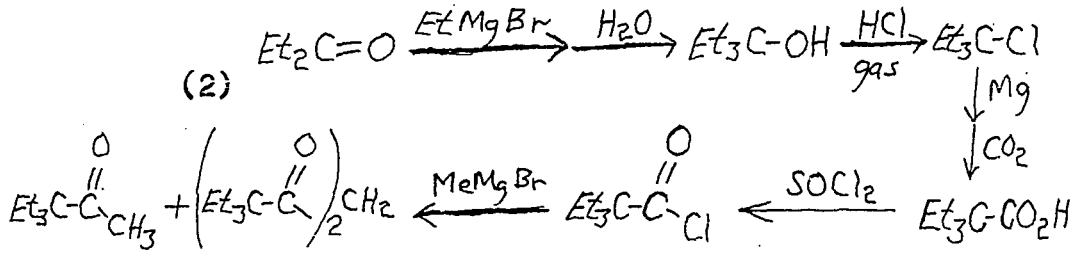
Historical

In attempting to prepare 2-methyl-3,3-diethylpentanol-2, by the action of methylmagnesium bromide on triethylacetyl chloride, Whitmore and Lewis (5) obtained instead two other compounds. One was methyl triethylcarbinyl ketone, obtained in 34% yield. The other, bis-triethylacetylmethane, was isolated in 32% yield as its copper derivative (chelate). The methyl ketone was found to give only enolization (abstraction of a methyl proton) upon treatment with methylmagnesium bromide (94% by measurement of the quantity of methane gas evolved). No addition of methyl to the carbonyl group occurred. This interesting chemical behaviour, usually observed with higher molecular weight ketones (6), is attributed to shielding of the carbonyl function by the bulky triethylcarbinyl group. Loening et al. (7) have observed that an ethyl group in a position alpha to the carbonyl group has a greater retarding effect on the rates of esterification than do two similarly situated methyl groups.

Thus, steric hindrance to carbonyl addition accounts for the unusual course of reaction of triethylacetyl chloride with methyl Grignard reagent. One methyl group adds readily, but the second does not. Instead, hydrogen abstraction of a methyl proton forms an enolate anion. This anion can itself attack triethylacetyl chloride, and forms, thereby, the beta-diketone. The outline of Whitmore's procedure leading to bis-triethyl-

acetylmethane is presented in reaction sequence (2):

(2)



Dipivaloylmethane (bis-trimethylacetylmethane), the methyl analogue of bis-triethylacetylmethane, has been prepared by Hauser et al. (8,9) from pinacolone (trimethylcarbinylmethyl ketone) and ethyl trimethylacetate (ethyl pivalate) by the use of sodium amide for the condensing agent. Yields of 28% (8) and 64% (9) were reported. Hauser et al. (8,9,10) used two methods which differed in the relative amounts of ketone, ester, and sodium amide to effect condensation to beta-diketone. This reaction has wide application for the synthesis of a variety of beta-diketones, both symmetrical and unsymmetrical (10). Recently Reeder (11), using lithium rather than sodium amide, improved upon the procedure of Hauser and Adams (8). In this method, the lithium chelate can be extracted from the reaction mixture using ether (the lithium chelate is only sparingly soluble in this solvent). The beta-diketone is generated from the chelate by acidification. The yield was 87%.

Hauser et al. (12) have prepared diisovalerylmethane from methyl isobutyl ketone and ethyl isovalerate using both of their methods A and B (10) in 75-76% yield. This beta-diketone (bis-isopropylacetylmethane) is somewhat less hindered than

bis-tertiarybutylacetylmethane, but it should provide some basis for estimation of yields to be obtained in the synthesis of the tertiarybutyl compound.

A method which has received little attention in view of the work of Hauser et al. (10) is that of Brändström (13), and, because of its simplicity, it may well prove to be of value for the synthesis of sterically-hindered beta-diketones. Specifically, he has prepared bis-diethylacetylmethane. In his procedure, diethyl malonate, the appropriate acid anhydride, and small amounts of magnesium oxide and copper acetate are mixed, and the mixture is distilled through a Widmer column. The method depends upon a Mass-Law effect by continuous removal of ethyl ester. Yields were 50-65%. Brändström prepared the requisite anhydrides in yields over 90% by refluxing the acid and half an equivalent of thionyl chloride for a period of about forty hours.

Within the last ten years two general methods for preparation of trialkylacetic acids have been reported. Sperber et al. (14) prepared a large number of various tri-substituted acetic acids by the alkylation of acetonitrile with the appropriate alkyl halide. The base which effected the condensation was sodium amide. It was necessary to hydrolyse the resulting trialkylacetonitrile to obtain the acid. For nitriles hydrolysed only with difficulty, sulfuric acid (80%) converted the nitrile to the amide. The amide was then treated with butyl

nitrite or nitrous anhydride to produce the acid. Over-all yields were 17-56%.

Schuerch and Huntress (15) alkylated acetonitrile with ethyl bromide in the presence of sodium amide. They obtained a mixture of the mono-, di-, and tri-ethylacetonitrile. The triethylacetonitrile obtained in a single run amounted to a quarter of a mole. The reaction required three moles of sodium amide. The nitrile was converted to the acid in 81% yield by hydrolysis with 75% sulfuric acid followed by treatment with sodium nitrite in 81% yield. Triethylacetamide was a by-product (17%) which could again be subjected to hydrolytic conditions leading to the acid.

In their method, Hauser and Chambers (16) also use an alkali amide-catalysed alkylation. The substrate for alkylation in this case was a tertiary ester of the appropriate dialkylacetic acid. Attack by amide ion at the carbonyl was blocked by use of a relatively large tertiary alkoxy group. With attack at the carbonyl position blocked, the only reaction possible for the amide ion was abstraction of the proton alpha to the ester carbonyl. Alkylation then proceeded at this position. It is not surprising, in view of the previous discussion, that the tertiary ester chosen by Hauser was the triethylcarbinyl ester. The product of the alkylation, a tertiary ester of the desired trialkylacetic acid, is readily hydrolysed in strong acid.

In the preparation of triethylcarbinyl esters, triethylcarbinol was converted to its sodium salt with sodium amide and then treated with dialkylacetylchloride. Triethylcarbinyl diethylacetate was prepared in 80% yield from diethylacetyl chloride and the anion from triethylcarbinol. This method of preparation of highly hindered esters is far superior to the usual methods, which do not give over 20% of triethylcarbinyl diethylacetate. This particular dialkyl acetate was converted in 80% yield to diethyl-n-butylacetic acid. The over-all yield based on diethylacetic acid was 61%. This method has a greater scope of application than other general methods now known.

Synthesis of carboxylic acids from olefins, and carbon monoxide, is not a new reaction. The reaction usually is carried out at high pressures. Recently, however, H. Koch (17) reported preparation of acids from tri- and tetra- substituted olefins at atmospheric pressure and room temperature. Carbon monoxide is generated in situ by addition of formic acid to a mixture of the olefin and 95% sulfuric acid. Details were not given in the abstract.

Whitmore and Lewis (5) prepared triethylacetic acid, which was used in the reaction leading to methyl triethylcarbinyl ketone and bis-triethylacetylmethane, by the standard method of carbonation of the Grignard reagent from the appropriate alkyl halide. Yields were not reported, but it would appear from other work by Whitmore and his co-workers that the

yields were quite low. Thus, triethylcarbinylmagnesium chloride was prepared in 58% yield (18) from triethylcarbinyl chloride, but reaction of the Grignard reagent with formaldehyde resulted in only 10% yield of primary alcohol. Whitmore and Badertsher (18) did report a 42% yield in the preparation of dimethylethylacetic acid on a three mole run. The yield was based on alkyl chloride used. For comparison purposes, it is noted that dimethyl-n-butylmagnesium chloride (19) was prepared in 60% yield, heptenes being by-products. This Grignard reagent was reacted with formaldehyde to 41-63% of primary alcohol. Whitmore et al. (20) converted isooctyl chloride to the Grignard compound in 52% yield, and carbonated the product to obtain the acid. The yield of dimethylneopentylacetic acid was 34%. Whitmore and Lux (21) prepared trimethylacetic acid in 75% yield, based on tertiary butyl chloride, in a nine mole run.

Whitmore et al. (22) oxidized diisobutylene with sodium dichromate and sulfuric acid to obtain methylneopentyl ketone. In a large scale reaction, Whitmore and Moersch (23) prepared eight kilograms (38% yield) of methylneopentyl ketone from 207 kilograms of diisobutylene.

Whitmore et al. (23,24) oxidized methylneopentyl ketone with sodium hypobromite to tertiarybutylacetic acid (80-90% yield).

Experimental

Bis-tertiarybutylacetylmethane

The procedure for the preparation of neopentylchloride, starting material in the synthesis of bis-tertiarybutylacetylmethane, was worked out satisfactorily with the assistance of Mr. Richard Hartley. Two to two and one-half liters of neopentane (Phillips Petroleum 99.9%) were chlorinated in a three liter flask cooled in an ice bath. Neopentane was introduced into the flask either directly from the tank, or from a two liter flask used to store neopentane (unreacted material from previous runs) in the refrigerator. The reaction mixture was stirred as chlorine was bubbled in slowly at such a rate as to keep the neopentane refluxing at a height of an inch in the Dry-Ice condenser. The reaction would not start until the neopentane had been saturated with chlorine gas. Care had to be taken that chlorine was not bubbled in too fast before the reaction had commenced, or the reaction would commence suddenly and violently. Charring would then occur. The reaction mixture was illuminated directly by an ordinary 150 watt electric bulb. Chlorine was bubbled into the solution, maintaining moderate reflux, for seven hours after the reaction was initiated. Unreacted neopentane was then removed by distillation by replacing the ice bath first with lukewarm water, and then with warmer water. The neopentane was condensed in a flask contained in an ice bath, and was stored in the refrigerator for future

use. The reaction mixture was washed twice with two hundred milliliters of 50% aqueous sulfuric acid and once with water, and then was dried over anhydrous potassium carbonate for twenty-four hours. Six hundred milliliters of impure neopentylchloride was obtained. This material was distilled. A forerun of about fifty milliliters of neopentane was collected in a Dry-Ice trap attached to the condenser of the column. The boiling range of the neopentyl chloride fraction was 83.5-84.5° at atmospheric pressure. The refractive index was $n_D^{24.5}$ 1.4022.

Neopentylchloride was converted to the Grignard reagent according to the procedure of Whitmore and Badertsher (18) for highly hindered alkyl halides. Runs were usually carried out with two to three moles of alkyl halide. Carbonation of the Grignard reagent was accomplished by pouring an ether solution of the Grignard reagent into a slurry of Dry-Ice in anhydrous diethyl ether. Work-up using extraction with base, and regeneration of the acid, followed by distillation at reduced pressure was found to be the best procedure. In one reaction carbon dioxide gas was bubbled through the solution of the Grignard reagent. The yield was 46%. On other runs yields were 55-65%.

Tertiarybutylacetic acid was converted to the acid chloride with thionyl chloride in 93% yield. Eastman White Label thionyl chloride gave better yields by about 10% than were

obtained with reagent obtained from other sources.

Whitmore et al. (24) prepared the ethyl ester of tertiarybutylacetic acid from the acid chloride in nearly quantitative yields. Yields in this work were 83% and lower.

Methyl neopentyl ketone was prepared by the oxidation of diisobutylene (99 mole percent 2,4,4-trimethylpentene-1; Phillips Petroleum Co.) with sulfuric acid and sodium dichromate according to the procedure of Whitmore et al. (22).

The condensation of methyl neopentyl ketone with ethyl tertiarybutyl acetate was carried out twice with sodium amide. Low yields of bis-tertiarybutylacetylmethane, b.p. 125-127° at 21 mm., were obtained. In one run methylmagnesium bromide was used as the base, but only trace amounts of copper chelate of the beta-diketone were found. In the one successful reaction, one mole of ester, two moles of diketone, and two and one-half moles of lithium were used, following the procedure of Hauser et al. (10) with modifications as suggested by Reeder (11). In the work-up, the lithium salt (chelate) of the beta-diketone was extracted directly from the reaction mixture with large quantities of ether. The ether solutions were then extracted with aqueous lithium hydroxide to remove any tertiarybutylacetic acid. The ether solutions of the lithium salt of the beta-diketone were then shaken with 5N sulfuric acid in a separatory funnel. This converted the chelate to the beta-diketone. The ether solutions of the beta-diketone were dried

with Drierite and the ether removed by distillation. The bis-tertiarybutylacetylmethane so obtained was distilled in vacuo in a Vigreaux distillation apparatus. The boiling range was 125-127° at about 20 mm. pressure. The refractive index was 1.457 at 27°. The 180 grams collected represent an 85% yield (based on ethyl tertiarybutylacetate). The material was pale yellow.

The pale yellow bis-tertiarybutylacetylmethane was stored in a brown bottle for three months. At this time a small sample was distilled through a small spinning band column. The material boiled over the range 107-110° at 5 mm. The refractive index was roughly 1.459 at about 22°. Three months later the main part of the material was distilled through a tantalum spiral wire column. Three fractions were collected over the range 73-77° at 2 mm. The refractive index for the first fraction was 1.4593, and for the third fraction it was 1.4597, both at 25°. The infra-red spectra of the three fractions were essentially identical. The third fraction was titrated potentiometrically in pyridine using tri-ethyl-n-butylammonium hydroxide in 90% benzene-10% methanol as the titrant. Values for the neutralization equivalent were near 330. The calculated value for bis-tertiary-butylacetylmethane is 212. The third fraction was distilled through a small center rod column. It could not be ascertained whether or not equilibrium had been attained, but three fractions were collected. The results are: 1) 94-97° at 4 mm., N. E. 315;

2) 65-67° at 2 mm., N. E. 322; 3) 67° at 2 mm., N. E. 344. The neutralization equivalent of the pot residue was 406. The conclusion was that the compound was not pure, nor was its purity improved in these distillations.

Bis-triethylacetylmethane

Various bases were used in attempts to alkylate acetonitrile with ethyl bromide. These were potassium tertiary butoxide, sodium hydride, and tertiarybutylmagnesium chloride. The reactions yielded only condensation products of acetonitrile, apparently, and no triethylacetonitrile. Use of sodium amide as in the procedure by Schuerch and Huntress (15) led to the desired product. The procedure of Schuerch led to the formation of one-quarter mole of triethylacetonitrile. This yield was improved* upon by using five moles of sodamide (rather than three), one and one-quarter moles of acetonitrile (rather than one and one-half moles), and six moles of ethyl bromide (rather than four and one-half moles). A mixture of ethyl bromide and acetonitrile was added to the sodium amide suspension. The run yielded about a quarter mole of material with a boiling range 170-175° and one-half mole of material boiling at 175-177°. The latter was assumed to be fairly pure triethylacetonitrile while the former was believed to be predominantly triethylacetonitrile with some diethylacetonitrile

*Suggested by Dr. Ernest Wenkert, Iowa State College, Ames, Iowa, 1956.

with some diethylacetonitrile present. The yield has been improved by at least a factor of two.

One hundred and thirty-two grams of triethylacetonitrile (Ref. Index; 1.4200 at 25.2°) was hydrolysed with sulfuric acid and sodium nitrite to triethylacetic acid according to the procedure used by Schuerch and Huntress (15). Neutralization equivalent of the acid was 144 ± 1%. The calculated value is 144.

From this triethylacetic acid, 144 grams of triethylacetyl chloride were prepared. The refractive index at 19.9° was 1.4438. This agrees exactly with that found by Whitmore and Lewis (5).

The triethylacetyl chloride (0.88 moles) was added to an ether solution of methylmagnesium iodide (2.8 moles). The procedure differed from that of Whitmore and Lewis (5) in that the acid chloride was added to the Grignard reagent, and the ratio of methyl halide to acid chloride was about 3 to 1 rather than 2 to 1. The reaction was allowed to proceed for about twenty hours before hydrolysis. These conditions, thought to be optimum for formation of bis-triethylacetylmethane, turned out to be forcing conditions for formation of tertiary alcohol (addition of the second molecule of methylmagnesium iodide to the carbonyl function did occur). No beta-diketone was found, and only two to three milliliters of methyl triethylcarbinyl ketone was isolated. A mixture of olefins was obtained. These products must have resulted from elimination of water from the

dimethyl tertiary carbinol during the work-up with acid.

Triethylcarbinyl ester of diethyl acetic acid* (1.42 moles, 48% yield) was prepared, according to the procedure of Hauser and Chambers (16) who obtained 80% yield. This reaction was run later with 3.1 moles of diethylacetyl chloride to give 2.4 moles of tricarbinyl ester (78% yield).

Triethylcarbinyl diethylacetate (1.4 moles) was treated with ethyl bromide (2.4 moles) in the presence of sodium amide (2.8 moles). There was produced about 1.2 moles of crude triethylcarbinyl triethylacetate. When the ester was hydrolysed, however, only one-third of a mole of triethylacetic acid, boiling range 132-135° at 27 mm., was obtained.

In another run, 1.1 moles (233 grams) of triethylcarbinyl diethylacetate was reacted with 4 moles of sodium amide and 2.1 moles of ethyl bromide. The triethylcarbinyl triethylacetate was not isolated, but was hydrolysed directly. One hundred grams (0.69 moles) of triethylacetic acid, boiling range 122-125° at 15-17 mm., was formed. This represented a 62% yield. Hauser and Chambers (16) obtained an 80% yield in a similar reaction using butyl bromide rather than ethyl bromide.

Attempted formation of the Grignard reagent from triethylcarbinyl chloride (2.85 moles) and subsequent carbonation gave

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*Two liters of diethylacetic acid were given to us by Carbide and Carbon Chemicals Company.

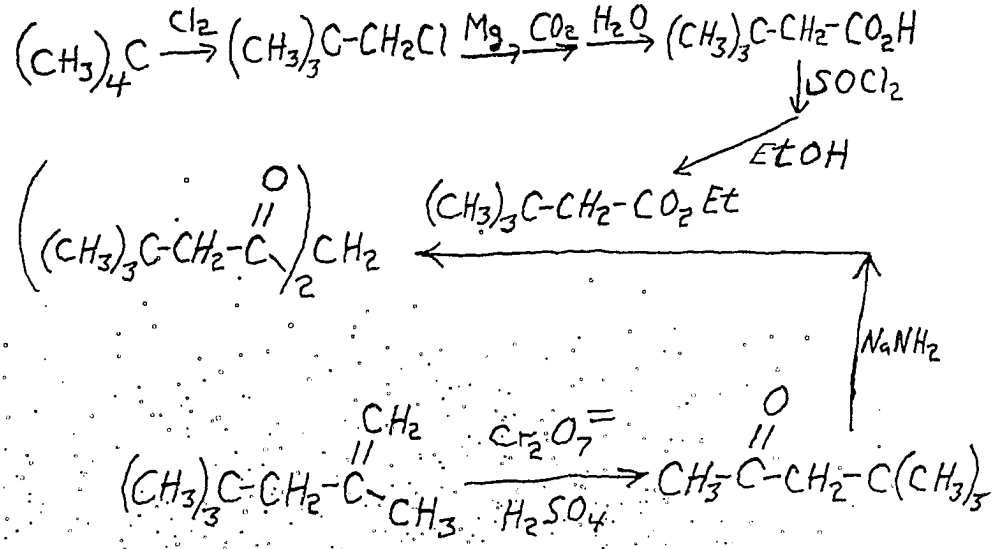
less than ten percent of impure triethylacetic acid. Attempts to prepare triethylcarbinyl lithium and triethylcarbinyl potassium were also unsuccessful. Bartlett and Lefferts (25) have prepared tertiarybutyl lithium. Bartlett and Schneider (26) have obtained products from the reaction of methyl pivalate with a solution containing sodium sand and tertiarybutyl chloride. Prior to addition of the ester, it appeared that no reaction between sodium and alkyl halide had occurred. Such a technique was not tried in this work.

3-Ethyl-2-pentene was mixed with sulfuric acid, and carbon monoxide, generated externally from formic acid and sulfuric acid, in an attempt to make triethylacetic acid after the manner of Koch (17). Two attempts were unsuccessful.

Discussion

The synthesis of bis-tertiarybutylacetylmethane was accomplished by the sequence of reactions represented in reaction sequence (3):

(3)



Each of these reactions is a good reaction in the sense that its manipulation is not prohibitively difficult; that it can be carried out on a fairly large scale of operation; that the chemicals involved are readily obtainable in high states of purity; and that relatively pure product can be obtained.

The chlorination of neopentane has been perfected almost as much as can be expected. One difficulty, the uncertainty in the initiation of the reaction, could be given some more attention; but the procedure had been developed to the point where the reaction routinely gave appreciable quantities of neopentyl chloride with little difficulty.

Preparation of neopentylmagnesium chloride, carbonation,

and hydrolysis are reactions that can be carried out on as large a scale as desired. Runs here were usually made with three moles of material. Better yields could be obtained, probably, by more careful manipulation in general. Use of tetrahydrofuran as a solvent in place of diethyl ether might lead to better yields.*

It should be possible to convert tertiarybutylacetic acid to its ethyl ester in higher yields than was accomplished in this work.

The preparation of methyl neopentyl ketone by oxidation of diisobutylene is not difficult although the reaction does take ten days. The reaction time could, perhaps, be shortened; but reliable results were obtained by following Whitmore's procedure closely. Steam distillation separates the desired methyl ketone from a complex reaction mixture conveniently.

The condensation of methylneopentyl ketone with ethyl tertiarybutylacetate, using lithium amide, gave an 85% yield. This could probably be improved.

The 85% yield mentioned assumes that the difficulty with the purity of the beta-diketone occurred because of decomposition over a period of time, and during the distillations. This may not have been the case. It is possible that the beta-diketone was not obtained pure in the first place. This should

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*Brooks, H. G. and Hughes, Mark. Chemistry Department, Iowa State College, Ames, Iowa. Private communication.

be investigated further. It would be necessary to perform a careful distillation shortly after the initial work-up. If it is found necessary, purification might be effected by forming the copper salt, recrystallizing from xylene, and regenerating the beta-diketone under mildly acid conditions. Distillation in a good fractionating column should be sufficient for final purification.

No method used to obtain triethylacetic acid was quite satisfactory. The total quantity of triethylacetonitrile that could be obtained in a given run could never exceed three-fourths of a mole since the five moles of sodium amide required represents about the maximum quantity with which it is convenient to work. With large amounts of sodium amide, hydrolysis of the reaction mixture must be done carefully since unreacted sodium lines the walls of the flask. One advantage of the procedure using alkylation of acetonitrile is the relative simplicity of work-up after the hydrolysis. Careful distillation separates the trialkylate from the lower alkylates. Conversion of the triethylacetonitrile to triethylacetic acid goes as smoothly as reported by Schuerch and Huntress (15).

The procedure of Hauser and Chambers (16) looks the most promising in terms of size of runs that can be made. The limiting reaction would be the alkylation of the triethylcarbinyl ester of diethylacetic acid. One can propose, on the basis of the two runs made, that two and one-half moles of

triethylcarbinyl diethylacetate could be reacted with five moles of sodium amide, and then with five moles of ethyl bromide to yield nearly two moles of triethylcarbinyl triethylacetate.

The hydrolysis step gave this worker much difficulty. However, it should be possible to recover any unhydrolysed ester, and re-subject it to hydrolysis. One low yield reaction in a long sequence of reactions, as here, cuts down the value of the procedure considerably. In the hands of an experienced worker, this should give high yields of large quantities of triethyl acetic acid.

It might be possible to obtain high yields of triethylcarbinyl magnesium chloride by preparing the Grignard reagent in tetrahydrofuran rather than in diethyl ether. If the overall reaction to triethylacetic acid could be made to go in even 30 percent yield, this might well be the method of choice. Whitmore and his co-workers routinely ran Grignard reactions in nine mole quantities. The triethylcarbinyl chloride needed for this reaction is readily prepared either from triethylcarbinol or 3-ethyl-2-pentene by treatment with concentrated hydrochloric acid (27).

The methyl triethylcarbinyl ketone needed in the synthesis of bis-triethylacetylmethane could be made from triethylacetyl chloride in a variety of ways. The method of choice probably would be inverse addition of methylmagnesium bromide to tri-

ethylacetyl chloride since, as observed by Whitmore and Lewis (5), the side product would be the desired compound, bis-triethylacetylmethane.

Summary

Bis-tertiarybutylacetylmethane was synthesized by a sequence of reactions which were not difficult experimentally, which could be used for preparation of large quantities of materials, and which gave products which were readily purified.

For the preparation of small amounts (one-quarter mole) of triethylacetic acid, the method of Schuerch and Huntress (15) was found to be less complicated than the procedure of Hauser and Chambers (16). Larger amounts of triethylacetic acid were prepared by the procedure of Hauser and Chambers (16).

It was found that in the preparation of bis-triethylacetylmethane inverse addition of methylmagnesium chloride to triethylacetyl chloride (Whitmore and Lewis, 5) is important. Addition of the acid chloride to the Grignard reagent resulted in formation of tertiary alcohol rather than the desired beta-diketone.

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Acknowledgments

The enthusiasm of Dr. George S. Hammond for this work, and for research in general, has been an inspiration for the author.

Mr. Anthony J. Moye advised the author on procedures for analyses in non-aqueous media. Discussions with Mr. Moye proved to be of great value.

Mr. Donald H. Froemsdorf graciously provided use of the gas-liquid-partition-chromatograph which he had constructed. His interest in this work and his critical comments were certainly appreciated.

Messrs. Charles E. Lang and Joseph Kivel generously allowed the author to use their Consolidated Electrodynamics Corporation gas chromatograph.

Mr. William A. Bappe provided some key compounds for this work. His general knowledge of reactivity of diazomethane helped the author in his choice of an analytical method.

Mr. Gerald L. Brennan provided advice and equipment for the boron trifluoride experiments.

Mr. Richard Hartley helped prepare several compounds necessary for the synthesis of bis-tertiarybutylacetylmethane.

Messrs. Barney M. Kadis, William M. Moore, and Richard Hartley enabled the author to carry out these experiments in an atmosphere of fine music.

Barbara provided the encouragement which enabled this

work to be carried out.

The author wishes to express his gratitude to these people. Working with them has certainly been a pleasure.